(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 03/084473 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US03/10632

(22) International Filing Date: 4 April 2003 (04.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/370,827 8 April 2002 (08.04.2002) US
60/417,202 9 October 2002 (09.10.2002) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARNETT, Stanley, F.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **DEFEO-JONES, Deborah** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HASKELL, Kathleen, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HUBER, Hans, E.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **NAHAS, Deborah, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **LINDSLEY, Craig, W.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ZHAO, Zhijian** [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HARTMAN, George, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/084473 A2

(54) Title: METHOD OF TREATING CANCER

(57) Abstract: The present invention is directed to a method of treating cancer which comprises administration of a compound which selectively inhibits the activity of one or two of the isoforms of Akt, a serine/threonine protein kinase. The invention is particularly directed to the method wherein the compound is dependent on the presence of the pleckstrin homology domain of Akt for its inhibitory activity.

TITLE OF THE INVENTION

METHOD OF TREATING CANCER

BACKGROUND OF THE INVENTION

The present invention relates to methods of treating cancer by selectively inhibiting one or more isoforms of Akt (also known as PKB, and referred to herein as either Akt or Akt/PKB). The present invention also relates to a method of identifying such compounds.

Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Aams et al. *Science*, 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase-7, caspase-8 and caspase-9 etc (Thorneberry et al. *Science*, 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell*, 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek et al., *Science*, 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (Ptdlns(3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell*, 81:727-736 (1995); Hemmings *Science*, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt/PKB mutants abolish survival-promoting activity of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases.

In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997). Analysis of Akt levels in human tumors showed that Akt-2 is overexpressed in a significant number of ovarian (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol. Chem.* 274:21528-21532 (1999).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Natl. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/PKBα, Akt2/PKBβ, and Akt3/PKBγ respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidylinositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1/PKBα occurs on two regulatory sites, Thr^{308} in the catalytic domain activation loop and on Ser^{473} near the carboxy terminus (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) and R. Meier *et al. J. Biol.Chem.*

272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2/PKBβ and Akt3/PKBγ. The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3'-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt/PKB near the carboxy terminus has not been identified yet, but a recent report implies a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PdtIns(3,4,5)-P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. No specific PDK1 inhibitors have been disclosed. Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams et al. *Curr. Biol.* 10:439-448 (2000).

It is therefore an object of the instant invention to provide a method for treating cancer that comprises administering an inhibitor of Akt/PKB activity that selectively inhibits one or more of the Akt/PKB isoforms over the other isoform(s).

It is also an object of the present invention to provide a method for treating cancer that comprises administering an inhibitor of Akt/PKB activity that selectively inhibits one or more of the Akt/PKB isoforms and is dependent on the PH domain, the hinge region of the protein or both the PH domain and the hinge region for its inhibitory activity.

It is also an object of the instant invention to provide a method of identifying an inhibitor of PKB that selectively inhibits one or more of the Akt/PKB isoforms and is dependent on the PH domain for its inhibitory activity.

SUMMARY OF THE INVENTION

The instant invention provides for a method of treating cancer which comprises administering to a mammal an inhibitor of Akt/PKB activity that electively inhibits one or more of the Akt/PKB isoforms. The invention also provides for a method of inhibiting Akt/PKB activity by administering a compound that is an inhibitor of Akt/PKB activity that selectively inhibits one or more of the Akt/PKB isoforms and is dependent on the PH domain for its inhibitory activity. A method of identifying such selective inhibitors of Akt/PKB activity is also disclosed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of inhibiting Akt/PKB activity which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound that selectively inhibits one or more of the Akt/PKB isoforms. The invention also relates to a method of treating cancer that comprises administering to a mammal in need thereof an inhibitor whose activity is dependent on the presence of the pleckstrin homology (PH) domain, the hinge region or both the PH domain and the hinge region of Akt.

Direct inhibition of one or more Akt isozymes provides the most specific means of regulating the PI3K/Akt pathway.

The term "inhibiting Akt/PKB activity" as used herein describes the decrease in the *in vitro* and *in vivo* biochemical modifications resulting from the phosphorylation of Akt by upstream kinases and/or the subsequent phosphorylation of downstream targets of Akt by activated Akt. Thus, the terms "inhibitor of Akt/PKB activity" and "inhibitor of Akt/PKB [isoforms]" describe an agent that, by binding to Akt, either inhibits the phosphorylation of Akt by upstream kinases (thereby reducing the amount of activated Akt) or inhibits the phosphorylation by activated Akt of protein targets of Akt, or inhibits both of these biochemical steps. In a preferred embodiment, the inhibitor utilized in the instant methods inhibits the phosphorylation of Akt by upstream kinases (thereby reducing the amount of activated Akt) and inhibits the phosphorylation by activated Akt of protein targets of Akt.

In an embodiment, the selective inhibitor useful in the instant method of treatment is selected from: a selective inhibitor of Akt1, a selective inhibitor of Akt2, a selective inhibitor of Akt3, a selective inhibitor of two of the three Akt isoforms or a selective inhibitor of all three Akt isoforms.

Preferably, the selective inhibitor useful in the instant method of treatment is selected from: a selective inhibitor of Akt1, a selective inhibitor of Akt2, a selective inhibitor of Akt3, a selective inhibitor of both Akt1 and Akt2, a selective inhibitor of both Akt1 and Akt3, or a selective inhibitor of both Akt2 and Akt3. More preferably, the selective inhibitor useful in the instant method of treatment is selected from: a selective inhibitor of Akt1, a selective inhibitor of Akt2 or a selective inhibitor of both Akt1 and Akt2.

Preferably, the selective inhibitor useful in the instant method is a small organic molecule. The term "small organic molecule", as used herein, refers to a compound that is an organic molecule of a size comparable to those organic molecules generally used in pharmaceuticals. The term excludes biological macromolecules (e.g., proteins, nucleic acids, etc.). Preferred small organic molecules range in size up to about 2000 Da, and more preferably in size up to about 1000 Da.

The term "selective inhibitor" as used herein is intended to mean that the inhibiting compound exhibits greater inhibition against the activity of the indicated isoform(s) of Akt, when compared to the compounds inhibition of the activity of the other Akt isoform(s) and other kinases, such as PKA and PKC. Preferably, the selectively inhibiting compound exhibits at least about a 5 fold greater inhibition against the activity of the indicated isoform(s) of Akt. More preferably, the selectively inhibiting compound exhibits at least about a 50 fold greater inhibition against the activity of the indicated isoform(s) of Akt.

In a second embodiment of the invention, the methods of treating cancer and inhibiting Akt comprise administering an inhibitor whose activity is dependent on the presence of the pleckstrin homology (PH) domain, the hinge region or both the PH domain and the hinge region of Akt.

The PH domains and hinge regions of the three Akt isoforms, though presumably functionally equivalent in terms of lipid binding, show little sequence homology and are much less conserved than the catalytic domains. Inhibitors of Akt that function by binding to the PH domain, the hinge region or both are thus able to discriminate between the three Akt isozymes.

A selective inhibitor whose inhibitory activity is dependent on the PH domain exhibits a decrease in *in vitro* inhibitory activity or no *in vitro* inhibitory activity against truncated Akt/PKB proteins lacking the PH domain.

A selective inhibitor whose inhibitory activity is dependent on the hinge region, the region of the proteins between the PH domain and the kinase domain (see Konishi *et al. Biochem. and Biophys. Res. Comm.* 216: 526-534 (1995), Figure 2, incorporated herein by reference), exhibits a decrease in *in vitro* inhibitory activity or no *in vitro* inhibitory activity against truncated Akt proteins lacking the PH domain and the hinge region or the hinge region alone.

The method of using such an inhibitor that is dependent on either the PH domain, the hinge region or both provides a particular advantage since the PH domains and hinge regions in the Akt isoforms lack the sequence homology that is present in the rest of the protein, particularly the homology found in the kinase domains (which comprise the catalytic domains and ATP-binding consensus sequences). It is therefore observed that certain inhibitor compounds, such as those described herein, are not only selective for one or two isoforms of Akt, but also are weak inhibitors or fail to inhibit other kinases, such as PKA and PKC, whose kinase domains share some sequence homology with the kinase domains of the Akt/PKB isoforms. Both PKA and PKC lack a PH domain and a hinge region.

Preferably, the selective inhibitor of the second embodiment is selected from: a selective inhibitor of Akt1, a selective inhibitor of Akt2 or a selective inhibitor of both Akt1 and Akt2.

In a sub-embodiment of the second embodiment, the selective inhibitor useful in the instant method of treatment is selected from: a selective inhibitor of Akt1, a selective inhibitor of Akt2, a selective inhibitor of Akt3 or a selective inhibitor of two of the three Akt isoforms.

In another sub-embodiment, the selective inhibitor of one or two of the Akt isoforms useful in the instant method of treatment is not an inhibitor of one or both of such Akt isoforms that have been modified to delete the PH domain, the hinge region or both the PH domain and the hinge region.

In another sub-embodiment, the selective inhibitor of all three Akt isoforms useful in the instant method of treatment is not an inhibitor of one, two or all of such Akt isoforms that have been modified to delete the PH domain, the hinge region or both the PH domain and the hinge region.

The present invention further relates to a method of identifying a compound that is a selective inhibitor of one or two of the Akt/PKB isoforms, or all three isoforms, whose inhibitory efficacy is dependent on the PH domain. The method comprises the steps of:

a) determining the efficacy of a test compound in inhibiting the activity of an Akt isoform;

b) determining the efficacy of the test compound in inhibiting the activity of the Akt isoform that has been modified to delete the PH domain; and

c) comparing the activity of the test compound against the Akt isoform with the activity of the test compound against the modified Akt isoform lacking the PH domain.

The present invention also relates to a method of identifying a compound that is a selective inhibitor of one or two of the Akt/PKB isoforms, or all three isoforms, whose inhibitory efficacy is dependent on the hinge region. The method comprises the steps of:

a) determining the efficacy of a test compound in inhibiting the activity of an Akt isoform;

b) determining the efficacy of the test compound in inhibiting the activity of the Akt isoform that has been modified to delete the PH domain;

c) determining the efficacy of the test compound in inhibiting the activity of the Akt isoform that has been modified to delete the PH domain and the hinge region; and

d) comparing the activity of the test compound against the Akt isoform, the activity of the test compound against the modified Akt isoform lacking the PH domain, and the activity of the test compound against the modified Akt isoform lacking the PH domain and the hinge region.

The compounds that are identified by the methods described above as inhibitors of the activity of one or more Akt isoforms that are dependent on the presence of either or both the PH domain or hinge region of the Akt isoform will be useful in the methods of treatment disclosed herein. Such compounds may further be useful as components in assay systems that may be used to identify other inhibitors of the activity of one or more Akt isoforms wherein the other inhibitors have inhibitory activity through selective binding and/or interaction with the kinase region of the Akt isoform(s). Also useful as an assay component would be a PH domain and/or hinge region dependent inhibitor that is an irreversible inhibitor of the Akt isoform(s). Methods are well known in the art for determining whether the activity of an inhibitor of a biological activity or enzyme is reversible or irreversible.

It is understood that the modified Akt isoforms useful in the above methods of identification may alternatively lack less than the full PH region and/or

hinge region. For example, a modified Akt isoform may lack the full PH domain and a portion of the hinge region. It is also understood that the methods may alternatively comprise modified Akt isoforms wherein the PH domain and/or the hinge region are modified by a specific point mutation(s) in those amino acid sequences. Such a method comprising a modified Akt isoform having a point mutation(s) in the PH domain and/or the hinge region may not only identify whether the activity of an inhibitor compound is dependent on the presence of the PH domain and/or the hinge region, but may also identify the specific site in the Akt isoform where the inhibitor compound interacts or binds with the protein.

The present invention is also directed to the cloning and expression of modified versions of the Akt isoforms that are useful in the methods of identifying inhibitor compounds described hereinabove. Specifically, modified Akt isoforms lacking only the PH domain (deletion of about aa 4-110 for Akt1, deletion of about aa 4-110 for Akt2 and deletion of about aa 4-109 for Akt3) may be prepared by techniques well known in the art. Similarly, modified Akt isoforms wherein both the PH domain and the hinge region are deleted (deletion of about aa 4-145 for Akt1, deletion of about aa 4-147 for Akt2 and deletion of about aa 4-143 for Akt3) may be prepared by techniques well known in the art.

The present invention is further directed to the cloning and expression of modified versions of the Akt isoforms wherein one or more point mutations are made to the amino acid sequences of the PH domain and the hinge region. Preferably, one or two point mutations are made to the amino acid sequences of the PH domain and the hinge region. Most preferably, one point mutation is made to the amino acid sequences of the PH domain and the hinge region.

The methods of the instant invention are useful in the treatment of cancer, in particular cancers associated with irregularities in the activity of PTEN, Akt and/or GSK3. Such cancers include, but are not limited to colon, prostate, colorectal, ovarian, pancreatic and breast cancer.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropyl-cellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyl-eneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived

from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the instant invention may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the instant invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds useful in the instant method of treatment of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms

of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

The instant compounds may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

The selective inhibitors of Akt of the instant invention are also useful in combination with known therapeutic agents and anti-cancer agents. For example, instant selective inhibitors of Akt are useful in combination with known anti-cancer agents. Combinations of the presently disclosed selective inhibitors of Akt with other anti-cancer or chemotherapeutic agents are within the scope of the invention.

Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, and agents that interfere with cell cycle checkpoints. The instant selective inhibitors of Akt are particularly useful when co-administered with radiation therapy.

In an embodiment, the instant selective inhibitors of Akt are also useful in combination with known anti-cancer agents including the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen,

raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5•-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites, biological response modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteosome inhibitors and ubiquitin ligase inhibitors..

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide,

MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteosome inhibitors include but are not limited to lactacystin and MLN-341 (Velcade).

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797. In an embodiment the epothilones are not included in the microtubule inhibitors/microtubule-stabilising agents.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768 and WO 01/98278, and pending U.S. Ser. Nos. 60/338,779 (filed December 6, 2001),

60/338,344 (filed December 6, 2001), 60/338,383 (filed December 6, 2001), 60/338,380 (filed December 6, 2001), 60/338,379 (filed December 6, 2001) and 60/344,453 (filed November 7, 2001). In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK and inhibitors of Rab6-KIFL.

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinases, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1.

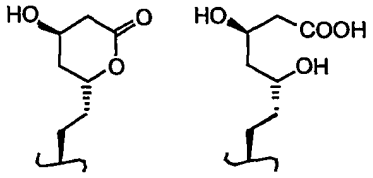
"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938,

4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone
I

Open-Acid
II

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. In an embodiment, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and in a further embodiment, simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as

those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl) methyl)-2-piperazinone, 5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{5-[4-hydroxymethyl-4-(4-

chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl} benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2'] bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclo-nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (±)-19,20-dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo [*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359.

For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Opthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin, Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925 (filed January 18, 2002).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are

specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

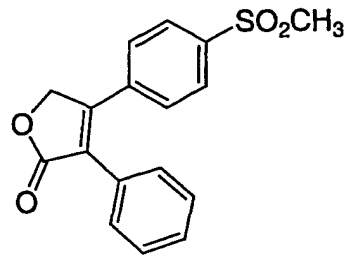
"Inhibitors of cell proliferation and survival signalling pathway" refer to compounds that inhibit signal transduction cascades downstream of cell surface receptors. Such agents include inhibitors of serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059), inhibitors of mTOR (for example Wyeth CCI-779), and inhibitors of PI3K (for example LY294002).

As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possess an IC_{50} for the inhibition of COX-2 of 1μM or less as measured by cell or microsomal assays.

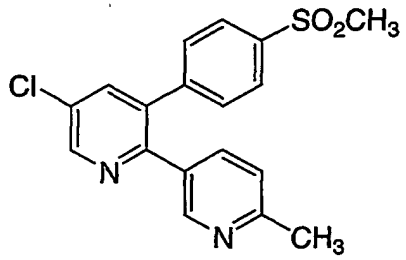
The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, issued December 12, 1995, U.S. Patent 5,861,419, issued January 19, 1999, U.S. Patent 6,001,843, issued December 14, 1999, U.S. Patent 6,020,343, issued February 1, 2000, U.S. Patent 5,409,944, issued April 25, 1995, U.S. Patent 5,436,265, issued July 25, 1995, U.S. Patent 5,536,752, issued July 16, 1996, U.S. Patent 5,550,142, issued August 27, 1996, U.S. Patent 5,604,260, issued February 18, 1997, U.S. 5,698,584, issued December 16, 1997, U.S. Patent 5,710,140, issued January 20,1998, WO 94/15932, published July 21, 1994, U.S. Patent 5,344,991, issued June 6, 1994, U.S. Patent 5,134,142, issued July 28, 1992, U.S. Patent 5,380,738, issued January 10, 1995, U.S. Patent 5,393,790, issued February 20, 1995, U.S. Patent 5,466,823, issued November 14, 1995, U.S. Patent 5,633,272, issued May 27, 1997, and U.S. Patent 5,932,598, issued August 3, 1999, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are:

3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and



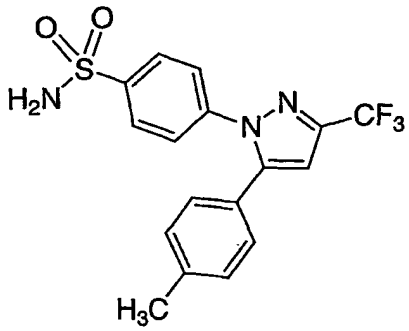
5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine;

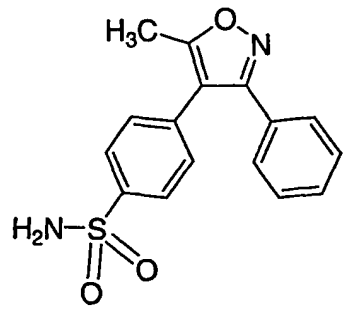


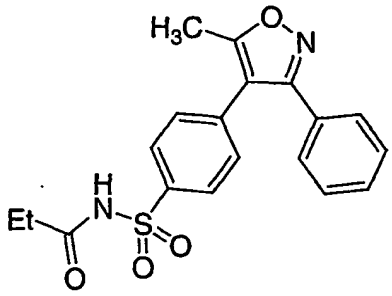
or a pharmaceutically acceptable salt thereof.

General and specific synthetic procedures for the preparation of the COX-2 inhibitor compounds described above are found in U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, and U.S. Patent No. 6,001,843, issued December 14, 1999, all of which are herein incorporated by reference.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following:







or a pharmaceutically acceptable salt thereof.

Compounds which are described as specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published July 21, 1994, U.S. Patent No. 5,344,991, issued June 6, 1994, U.S. Patent No. 5,134,142, issued July 28, 1992, U.S. Patent No. 5,380,738, issued January 10, 1995, U.S. Patent No. 5,393,790, issued February 20, 1995, U.S. Patent No. 5,466,823, issued November 14, 1995, U.S. Patent No. 5,633,272, issued May 27, 1997, and U.S. Patent No. 5,932,598, issued August 3, 1999.

Compounds which are specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, U.S. Patent No. 6,001,843, issued December 14, 1999, U.S. Patent No. 6,020,343, issued February 1, 2000, U.S. Patent No. 5,409,944, issued April 25, 1995, U.S. Patent No. 5,436,265, issued July 25, 1995, U.S. Patent No. 5,536,752, issued July 16, 1996, U.S. Patent No. 5,550,142, issued August 27, 1996, U.S. Patent No. 5,604,260, issued February 18, 1997, U.S.

Patent No. 5,698,584, issued December 16, 1997, and U.S. Patent No. 5,710,140, issued January 20,1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e.,

PPAR-delta) agonists are useful in the treatment of certain malingnancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed selective inhibitors of Akt in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am. J. Hum. Genet.* 61:785-789, 1997) and Kufe et al (Cancer Medicine, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," Gene Therapy, August 1998;5(8):1105-13), and interferon gamma (*J. Immunol.* 2000;164:217-222).

The selective inhibitors of Akt of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

The selective inhibitors of Akt of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including

acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a selective inhibitor of Akt of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S.Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. For the treatment or prevention of emesis that may result upon administration of the instant compounds, conjunctive therapy with an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is preferred.

Neurokinin-1 receptor antagonists of use in conjunction with the selective inhibitors of Akt of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844; 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203,

96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the selective inhibitors of Akt of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

The selective inhibitors of Akt of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin alfa).

The selective inhibitors of Akt of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

The selective inhibitors of Akt of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

Thus, the scope of the instant invention encompasses the use of the instantly claimed selective inhibitors of Akt in combination with a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic/cytostatic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,

9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) PPAR-γ agonists,
12) PPAR-δ agonists,
13) an inhibitor of inherent multidrug resistance,
14) an anti-emetic agent,
15) an agent useful in the treatment of anemia,
16) an agent useful in the treatment of neutropenia,
17) an immunologic-enhancing drug,
18) an inhibitor of cell proliferation and survival signaling, and
19) an agent that interferes with a cell cycle checkpoint.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a selective inhibitor of Akt of the instant invention in combination with radiation therapy and/or in combination with a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) a retinoid receptor modulator,
4) a cytotoxic/cytostatic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) PPAR-γ agonists,
12) PPAR-δ agonists,

13) an inhibitor of inherent multidrug resistance,
14) an anti-emetic agent,
15) an agent useful in the treatment of anemia,
16) an agent useful in the treatment of neutropenia,
17) an immunologic-enhancing drug,
18) an inhibitor of cell proliferation and survival signaling, and
19) an agent that interferes with a cell cycle checkpoint.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a selective inhibitor of Akt of the instant invention in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a selective inhibitor of Akt of the instant invention in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a selective inhibitor of Akt of the instant invention and a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) a retinoid receptor modulator,
4) a cytotoxic/cytostatic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) a PPAR-γ agonist,
12) a PPAR-δ agonist;
13) an inhibitor of cell proliferation and survival signaling, and
14) an agent that interferes with a cell cycle checkpoint.

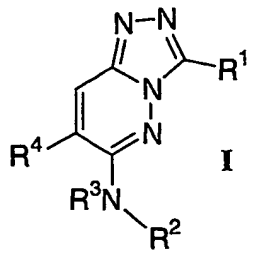
When a composition according to this invention is administered into

a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of an inhibitor of one, two or all three of the Akt/PKB isoforms is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount of inhibitor of between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day. A particular therapeutic dosage that comprises the instant composition includes from about 0.01 mg to about 1000 mg of inhibitor of Akt/PKB. Preferably, the dosage comprises from about 1 mg to about 1000 mg of inhibitor of Akt/PKB.

Compounds which are useful in the methods of treatment of the instant invention and are identified by the properties described hereinabove include:

i) a compound of the formula I:



I

wherein

R^1 represents phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted with one, two or three substituents, independently selected from:

a) halogen;

b) C_{1-4} alkyl;

c) C_{1-4} alkoxy;

d) cyano;

e) di(C_{1-4} alkyl)amino;

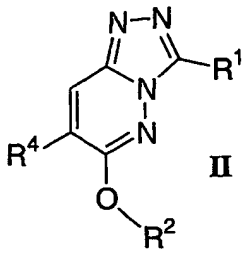
f) hydroxy;

R^2 represents amino-C_{1-6} alkyl, C_{1-4} alkylamino-(C_{1-6})alkyl, di(C_{1-4} alkyl)amino-(C_{1-6})alkyl, hydroxy-(C_{1-6})alkyl or C_{1-4} alkoxy-(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^3 represents hydrogen or C_{1-6} alkyl; and

R^4 is selected from: C_{3-7} cycloalkyl and aryl, any of which groups may be optionally substituted;

ii) a compound of the formula II:



II

wherein

R^1 represents phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted with one, two or three substituents, independently selected from:

a) halogen;

b) C_{1-4} alkyl;

c) C_{1-4} alkoxy;

d) cyano;

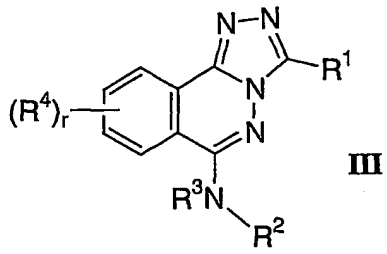
e) di(C_{1-4} alkyl)amino;

f) hydroxy;

R^2 represents amino-C_{1-6} alkyl, C_{1-4} alkylamino-(C_{1-6})alkyl, di(C_{1-4} alkyl) amino-(C_{1-6})alkyl, hydroxy-(C_{1-6})alkyl or C_{1-4} alkoxy-(C_{1-6})alkyl, any of which groups may be optionally substituted; and

R^4 is selected from: C_{3-7} cycloalkyl and aryl, any of which groups may be optionally substituted;

iii) a compound of the formula III:



III

wherein

R^1 represents phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted with one, two or three substituents, independently selected from:

a) halogen;

b) C_{1-4} alkyl;

c) C_{1-4} alkoxy;

d) cyano;

e) di(C_{1-4} alkyl)amino;

f) hydroxy;

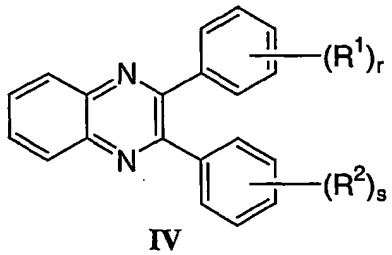
R^2 represents amino-C_{1-6} alkyl, C_{1-4} alkylamino-(C_{1-6})alkyl, di(C_{1-4} alkyl)amino-(C_{1-6})alkyl, hydroxy-(C_{1-6})alkyl or C_{1-4} alkoxy-(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^3 represents hydrogen or C_{1-6} alkyl; and

R^4 independently represents hydrogen, C_{1-6}-alkyl, halogen, HO- or C_{1-6} alkyl-O;

r is 1 or 2;

iv) a compound of the formula IV:



IV

wherein

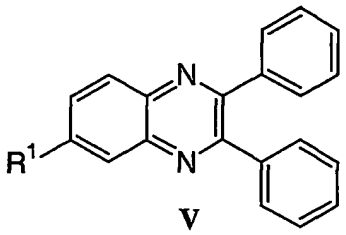
R^1 independently represents amino, C_{1-6}-alkyl amino, di-C_{1-6}-alkylamino, amino-C_{1-6} alkyl, C_{1-6} alkylamino-(C_{1-6})alkyl or di(C_{1-6} alkyl)amino-(C_{1-6})alkyl;

R^2 independently represents hydrogen, amino, C_{1-6}-alkyl amino, di-C_{1-6}-alkylamino, amino-C_{1-6} alkyl, C_{1-6} alkylamino-(C_{1-6})alkyl or di(C_{1-6} alkyl)amino-(C_{1-6}) alkyl;

r is 1 to 3;

s is 1 to 3;

v) a compound of the formula V:



V

wherein

R^1 independently represents hydrogen, C_{1-6}-alkyl, halogen, HO- or C_{1-6} alkyl-O;

or a pharmaceutically acceptable salt thereof.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy" are to be construed accordingly.

As used herein, the expression "C_{1-4} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl and *tert*-butyl. Derived expressions such as "C_{1-4} alkoxy" are to be construed accordingly.

Typical C_{3-7} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The expression "C_{3-7} cycloalkyl(C_{1-6})alkyl" as used herein includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

Typical C_{4-7} cycloalkenyl groups include cyclobutenyl, cyclopentenyl and cyclohexenyl.

Typical aryl groups include phenyl and naphthyl, preferably phenyl.

The expression "aryl(C_{1-6})alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine or chlorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope prodrugs of the compounds of formulae I-V above. In general, such prodrugs will be functional derivatives of the compounds of formulae I-V which are readily convertible *in vivo* into the required compound of formulae I-V. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds useful in the instant methods of treatment have at least one asymmetric center, they may accordingly exist as enantiomers. Where such compounds possess two or more asymmetric centers, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Examples of suitable values for the substituent R^4 include methyl, ethyl, isopropyl, *tert*-butyl, 1,1-dimethylpropyl, methyl-cyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, cyclobutenyl, phenyl, pyrrolidinyl, methyl-pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyridinyl, furyl, thienyl, chloro-thienyl and diethylamino.

In a particular embodiment, the substituent R^4 represents C_{3-7} cycloalkyl or phenyl, either unsubstituted or substituted by C_{1-6} alkyl, especially methyl. Favourably, Z represents cyclobutyl or phenyl.

Examples of typical optional substituents on the group R^1 include methyl, fluoro and methoxy.

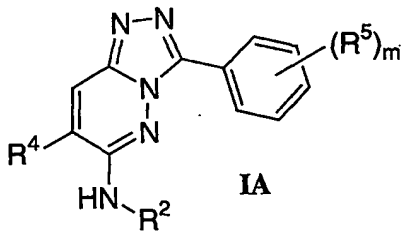
Representative values of R^1 include cyclopropyl, phenyl, methylphenyl, fluorophenyl, difluorophenyl, methoxyphenyl, furyl, thienyl, methylthienyl and pyridinyl.

In a particular embodiment, R^2 represents amino-C_{1-6} alkyl, C_{1-4} alkylamino-(C_{1-6})alkyl or di(C_{1-4} alkyl)amino-(C_{1-6})alkyl. Representative values of R^2 include but are not limited to dimethylaminomethyl, aminoethyl, dimethylaminoethyl, diethylaminoethyl, 3-dimethylaminopropyl, 3-methylaminopropyl, 3-dimethylamino-2,2-dimethylpropyl and , 3-dimethylamino-2-methylpropyl.

Suitably, R^3 represents hydrogen or methyl.

In a particular embodiment of the method of the instant invention, the compound that selectively inhibits one or two of the Akt/PKB isoforms is selected from:

i) a compound of the formula IA:



IA

wherein

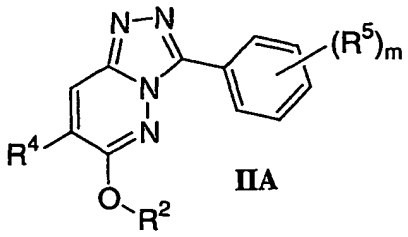
R^2 is as defined with reference to formula I above;

R^4 is selected from: C_{3-7} cycloalkyl and phenyl, any of which groups may be optionally substituted.

m is 0, 1, 2 or 3; and

R^5 independently represents halogen, C_{1-4} alkyl or C_{1-6} alkoxy;

ii) a compound of the formula IIA:



IIA

wherein

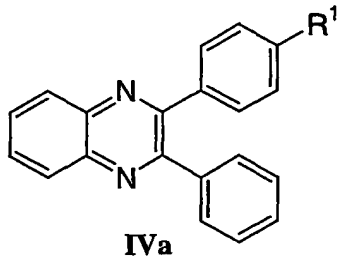
R^2 is as defined with reference to formula II above;

R^4 is selected from: C_{3-7} cycloalkyl and phenyl, any of which groups may be optionally substituted.

m is 0, 1, 2 or 3; and

R^5 independently represents halogen, C_{1-4} alkyl or C_{1-6} alkoxy;

iii) a compound of the formula IVa:



IVa

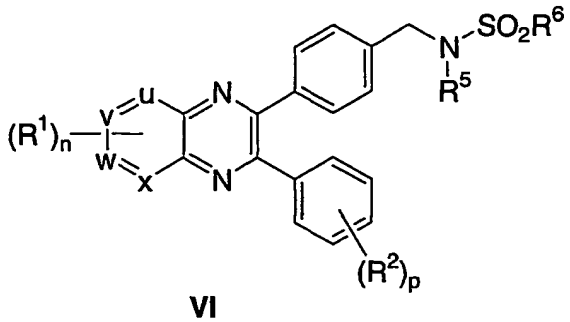
wherein

R^1 independently represents amino, C_{1-6}-alkyl amino, di-C_{1-6}-alkylamino, amino-C_{1-6} alkyl, C_{1-6} alkylamino-(C_{1-6})alkyl or di(C_{1-6} alkyl)amino-(C_{1-6})alkyl;

or the pharmaceutically acceptable salts thereof.

Other compounds which are useful in the methods of treatment of the instant invention and are identified by the properties described herein include:

i) a compound of the formula VI:



VI

wherein:

n is 0, 1, 2 or 3;

p is 0, 1 or 2;

r is 0 or 1;

s is 0 or 1;

u, v, w and x are independently selected from: CH and N, provided that only one of u, v, w and x may be N;

R^1 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
7) CO_2H,
8) halo,
9) CN,
10) OH,
11) O_bC_1-C_6 perfluoroalkyl,
12) $O_a(C=O)_bNR^7R^8$,
13) $NR^c(C=O)NR^7R^8$,
14) $S(O)_mR^a$,

15) $S(O)_2NR^7R^8$,
16) $NR^cS(O)_mR^a$,
17) oxo,
18) CHO,
19) NO_2,
20) $NR^c(C=O)O_bR^a$,
21) $O(C=O)O_bC_1$-C_{10} alkyl,
22) $O(C=O)O_bC_3$-C_8 cycloalkyl,
23) $O(C=O)O_b$aryl, and
24) $O(C=O)O_b$-heterocycle,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^z;

R^2 is independently selected from:

1) C_1-C_6 alkyl,
2) aryl,
3) heterocyclyl,
4) CO_2H,
5) halo,
6) CN,
7) OH,
8) $S(O)_2NR^7R^8$,

said alkyl, aryl and heterocyclyl optionally substituted with one, two or three substituents selected from R^z;

R^5 is independently selected from:

1) H,
2) C_1-C_{10} alkyl,
3) aryl, and
4) C_3-C_8 cycloalkyl,

said alkyl, cycloalkyl and aryl is optionally substituted with one or more substituents selected from R^z;

R^6 is NR^7R^8, (C_1-C_6)alkyl, (C_1-C_6)perfluoroalkyl, (C_3-C_6)cycloalkyl, noboranyl, aryl, 2,2,2-trifluoroethyl, benzyl or heterocyclyl, said alkyl, cycloalkyl, noboranyl,

aryl, heterocyclyl and benzyl is optionally substituted with one or more substituents selected from R^z;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1$-C_{10} alkyl,
3) $(C=O)O_bC_3$-C_8 cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) C_1-C_{10} alkyl,
7) aryl,
8) C_2-C_{10} alkenyl,
9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^z, or

R^z is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl,
2) $O_r(C_1$-$C_3)$perfluoroalkyl,
3) $(C_0$-$C_6)$alkylene-$S(O)_mR^a$,
4) oxo,
5) OH,
6) halo,
7) CN,
8) $(C=O)_rO_s(C_2$-$C_{10})$alkenyl,
9) $(C=O)_rO_s(C_2$-$C_{10})$alkynyl,
10) $(C=O)_rO_s(C_3$-$C_6)$cycloalkyl,
11) $(C=O)_rO_s(C_0$-$C_6)$alkylene-aryl,
12) $(C=O)_rO_s(C_0$-$C_6)$alkylene-heterocyclyl,
13) $(C=O)_rO_s(C_0$-$C_6)$alkylene-$N(R^b)_2$,
14) $C(O)R^a$,

15) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
16) C(O)H,
17) $(C_0\text{-}C_6)$alkylene-CO_2H,
18) $C(O)N(R^b)_2$,
19) $S(O)_mR^a$, and
20) $S(O)_2NR^9R^{10}$
21) $NR^c(C=O)O_bR^a$,
22) $O(C=O)O_bC_1\text{-}C_{10}$ alkyl,
23) $O(C=O)O_bC_3\text{-}C_8$ cycloalkyl,
24) $O(C=O)O_b$aryl, and
25) $O(C=O)O_b$-heterocycle,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^a is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, substituted or unsubstituted aryl, or heterocyclyl; and

R^b is H, $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted aryl, substituted or unsubstituted benzyl, substituted or unsubstituted heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C=O)OC_1\text{-}C_6$ alkyl, $(C=O)C_1\text{-}C_6$ alkyl or $S(O)_2R^a$;

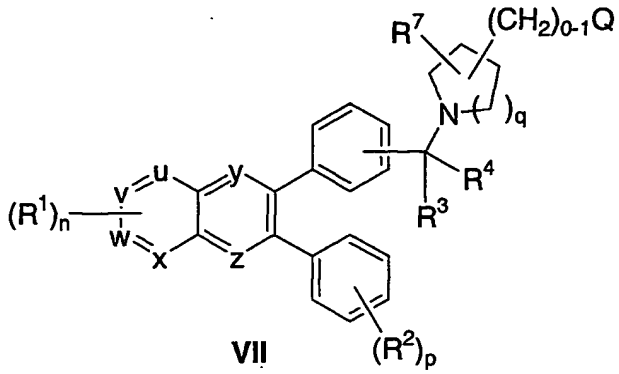
R^c is selected from:

1) H,
2) $C_1\text{-}C_{10}$ alkyl,
3) aryl,
4) $C_2\text{-}C_{10}$ alkenyl,
5) $C_2\text{-}C_{10}$ alkynyl,
6) heterocyclyl,
7) $C_3\text{-}C_8$ cycloalkyl,
8) $C_1\text{-}C_6$ perfluoroalkyl,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^z;

or a pharmaceutically acceptable salt thereof.

ii) a compound of the formula VII:



VII

wherein:

a is 0 or 1;
b is 0 or 1;
m is 0, 1 or 2;
n is 0, 1, 2 or 3;
p is 0, 1 or 2;
q is 0, 1, 2, 3 or 4;
r is 0 or 1;
s is 0 or 1;
t is 2, 3, 4, 5 or 6;

u, v, w and x are independently selected from: CH and N;

y and z are independently selected from: CH and N, provided that at least one of y and z is N;

Q is selected from: $-NR^5R^6$, aryl and heterocyclyl, said aryl and heterocycle which is optionally substituted with one to three R^z;

R^1 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,

3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
7) CO_2H,
8) halo,
9) CN,
10) OH,
11) O_bC_1-C_6 perfluoroalkyl,
12) $O_a(C=O)_bNR^5R^6$,
13) $NR^c(C=O)NR^5R^6$,
14) $S(O)_mR^a$,
15) $S(O)_2NR^5R^6$,
16) $NR^cS(O)_mR^a$,
17) oxo,
18) CHO,
19) NO_2,
20) $NR^c(C=O)O_bR^a$,
21) $O(C=O)O_bC_1$-C_{10} alkyl,
22) $O(C=O)O_bC_3$-C_8 cycloalkyl,
23) $O(C=O)O_b$aryl, and
24) $O(C=O)O_b$-heterocycle,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^z;

R^2 is independently selected from:
1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
7) CO_2H,
8) halo,

9) CN,
10) OH,
11) O_bC_1-C_6 perfluoroalkyl,
12) $O_a(C=O)_bNR^5R^6$,
13) $NR^c(C=O)NR^5R^6$,
14) $S(O)_mR^a$,
15) $S(O)_2NR^5R^6$,
16) $NR^cS(O)_mR^a$,
17) CHO,
18) NO_2,
19) $NR^c(C=O)O_bR^a$,
20) $O(C=O)O_bC_1$-C_{10} alkyl,
21) $O(C=O)O_bC_3$-C_8 cycloalkyl,
22) $O(C=O)O_b$aryl, and
23) $O(C=O)O_b$-heterocycle,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^z;

R^3 and R^4 are independently selected from: H, C_1-C_6-alkyl and C_1-C_6-perfluoroalkyl, or

R^3 and R^4 are combined to form $-(CH_2)_t-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from O, $S(O)_m$, $-N(R^b)C(O)-$, and $-N(COR^a)-$;

R^5 and R^6 are independently selected from:

1) H,
2) $(C=O)O_bR^a$,
3) C_1-C_{10} alkyl,
4) aryl,
5) C_2-C_{10} alkenyl,
6) C_2-C_{10} alkynyl,
7) heterocyclyl,
8) C_3-C_8 cycloalkyl,
9) SO_2R^a, and

10) $(C=O)NR^b_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^z, or

R^5 and R^6 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^z;

R^7 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
7) CO_2H,
8) halo,
9) CN,
10) OH,
11) O_bC_1-C_6 perfluoroalkyl,
12) $O_a(C=O)_bNR^5R^6$,
13) $NR^5(C=O)NR^5R^6$,
14) $S(O)_mR^a$,
15) $S(O)_2NR^5R^6$,
16) $NR^5S(O)_mR^a$,
17) oxo,
18) CHO,
19) NO_2,
20) $O(C=O)O_bC_1$-C_{10} alkyl, and
21) $O(C=O)O_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^z;

R^z is selected from:

1) $(C=O)_rO_s(C_1\text{-}C_{10})$alkyl,
2) $O_r(C_1\text{-}C_3)$perfluoroalkyl,
3) $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$,
4) oxo,
5) OH,
6) halo,
7) CN,
8) $(C=O)_rO_s(C_2\text{-}C_{10})$alkenyl,
9) $(C=O)_rO_s(C_2\text{-}C_{10})$alkynyl,
10) $(C=O)_rO_s(C_3\text{-}C_6)$cycloalkyl,
11) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-aryl,
12) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
13) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
14) $C(O)R^a$,
15) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
16) C(O)H,
17) $(C_0\text{-}C_6)$alkylene-CO_2H,
18) $C(O)N(R^b)_2$,
19) $S(O)_mR^a$,
20) $S(O)_2N(R^b)_2$
21) $NR^c(C=O)O_bR^a$,
22) $O(C=O)O_bC_1\text{-}C_{10}$ alkyl,
23) $O(C=O)O_bC_3\text{-}C_8$ cycloalkyl,
24) $O(C=O)O_b$aryl, and
25) $O(C=O)O_b$-heterocycle,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^a is substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_2\text{-}C_6)$alkenyl, substituted or unsubstituted $(C_2\text{-}C_6)$alkynyl, substituted or unsubstituted

$(C_3$-$C_6)$cycloalkyl, substituted or unsubstituted aryl, $(C_1$-$C_6)$perfluoroalkyl, 2,2,2-trifluoroethyl, or substituted or unsubstituted heterocyclyl; and

R^b is H, $(C_1$-$C_6)$alkyl, substituted or unsubstituted aryl, substituted or unsubstituted benzyl, substituted or unsubstituted heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C{=}O)OC_1$-C_6 alkyl, $(C{=}O)C_1$-C_6 alkyl or $S(O)_2R^a$;

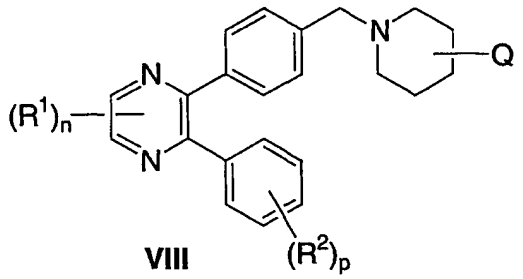
R^c is selected from:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_2-C_{10} alkenyl,
5) C_2-C_{10} alkynyl,
6) heterocyclyl,
7) C_3-C_8 cycloalkyl,
8) C_1-C_6 perfluoroalkyl,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^z,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

iii) a compound of the formula VIII:



VIII

wherein:

n is 0, 1 or 2;
p is 0, 1 or 2;
r is 0 or 1;

s is 0 or 1;

Q is selected from: -NR^7R^8 and heterocyclyl, the heterocyclyl optionally substituted with one or two R^z;

R^1 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
7) CO_2H,
8) halo,
9) CN,
10) OH,
11) O_bC_1-C_6 perfluoroalkyl,
12) $O_a(C=O)_bNR^7R^8$,
13) $NR^c(C=O)NR^7R^8$,
14) $S(O)_mR^a$,
15) $S(O)_2NR^7R^8$,
16) $NR^cS(O)_mR^a$,
17) oxo,
18) CHO,
19) NO_2,
20) $NR^c(C=O)O_bR^a$,
21) $O(C=O)O_bC_1$-C_{10} alkyl,
22) $O(C=O)O_bC_3$-C_8 cycloalkyl,
23) $O(C=O)O_b$aryl, and
24) $O(C=O)O_b$-heterocycle,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^z;

R^2 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,

2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
7) CO_2H,
8) halo,
9) CN,
10) OH,
11) O_bC_1-C_6 perfluoroalkyl,
12) $O_a(C=O)_bNR^7R^8$,
13) $NR^c(C=O)NR^7R^8$,
14) $S(O)_mR^a$,
15) $S(O)_2NR^7R^8$,
16) $NR^cS(O)_mR^a$,
17) CHO,
18) NO_2,
19) $NR^c(C=O)O_bR^a$,
20) $O(C=O)O_bC_1$-C_{10} alkyl,
22) $O(C=O)O_bC_3$-C_8 cycloalkyl,
23) $O(C=O)O_b$aryl, and
24) $O(C=O)O_b$-heterocycle,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^z;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1$-C_{10} alkyl,
3) $(C=O)O_bC_3$-C_8 cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) C_1-C_{10} alkyl,
7) aryl,
8) C_2-C_{10} alkenyl,

9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^z, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^z;

R^z is selected from:
1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl,
2) $O_r(C_1$-$C_3)$perfluoroalkyl,
3) $(C_0$-$C_6)$alkylene-$S(O)_mR^a$,
4) oxo,
5) OH,
6) halo,
7) CN,
8) $(C=O)_rO_s(C_2$-$C_{10})$alkenyl,
9) $(C=O)_rO_s(C_2$-$C_{10})$alkynyl,
10) $(C=O)_rO_s(C_3$-$C_6)$cycloalkyl,
11) $(C=O)_rO_s(C_0$-$C_6)$alkylene-aryl,
12) $(C=O)_rO_s(C_0$-$C_6)$alkylene-heterocyclyl,
13) $(C=O)_rO_s(C_0$-$C_6)$alkylene-$N(R^b)_2$,
14) $C(O)R^a$,
15) $(C_0$-$C_6)$alkylene-CO_2R^a,
16) C(O)H,
17) $(C_0$-$C_6)$alkylene-CO_2H,
18) $C(O)N(R^b)_2$,
19) $S(O)_mR^a$,

20) $S(O)_2NR^9R^{10}$
21) $NR^c(C=O)O_bR^a$,
22) $O(C=O)O_bC_1$-C_{10} alkyl,
23) $O(C=O)O_bC_3$-C_8 cycloalkyl,
24) $O(C=O)O_b$aryl, and
25) $O(C=O)O_b$-heterocycle,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1$-$C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1$-C_6 alkyl, oxo, and $N(R^b)_2$;

R^a is $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl, substituted or unsubstituted aryl, $(C_1$-$C_6)$perfluoroalkyl, 2,2,2-trifluoroethyl, or substituted or unsubstituted heterocyclyl; and

R^b is H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)OC_1$-C_6 alkyl, $(C=O)C_1$-C_6 alkyl or $S(O)_2R^a$;

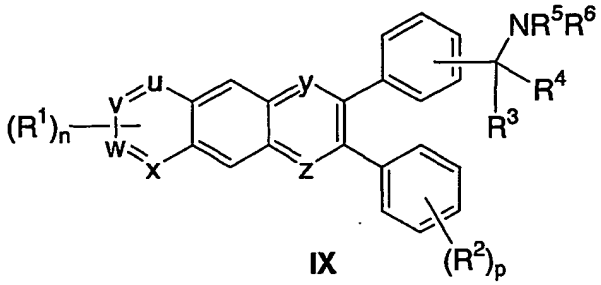
R^c is selected from:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_2-C_{10} alkenyl,
5) C_2-C_{10} alkynyl,
6) heterocyclyl,
7) C_3-C_8 cycloalkyl,
8) C_1-C_6 perfluoroalkyl,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^z, or

or a pharmaceutically acceptable salt or a stereoisomer thereof.

iv) a compound of the formula IX:



IX

wherein:

a is 0 or 1;
b is 0 or 1;
m is 0, 1 or 2;
n is 0, 1 or 2;
p is 0, 1, 2 or 3;
r is 0 or 1;
s is 0 or 1;
t is 2, 3, 4, 5 or 6;

u, v and x are independently selected from: CH and N;

w is selected from a bond, CH and N;

y and z are independently selected from: CH and N, provided that at least one of y and z is N;

R1 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

7) CO_2H,
8) halo,
9) CN,
10) OH,
11) O_bC_1-C_6 perfluoroalkyl,
12) $O_a(C=O)_bNR^7R^8$,
13) $NR^c(C=O)NR^7R^8$,
14) $S(O)_mR^a$,
15) $S(O)_2NR^7R^8$,
16) $NR^cS(O)_mR^a$,
17) oxo,
18) CHO,
19) NO_2,
20) $NR^c(C=O)O_bR^a$,
21) $O(C=O)O_bC_1$-C_{10} alkyl,
22) $O(C=O)O_bC_3$-C_8 cycloalkyl,
23) $O(C=O)O_b$aryl, and
24) $O(C=O)O_b$-heterocycle,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^z;

R^2 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
7) CO_2H,
8) halo,
9) CN,
10) OH,
11) O_bC_1-C_6 perfluoroalkyl,
12) $O_a(C=O)_bNR^7R^8$,

13) $NR^c(C=O)NR^7R^8$,
14) $S(O)_mR^a$,
15) $S(O)_2NR^7R^8$,
16) $NR^cS(O)_mR^a$,
17) CHO,
18) NO_2,
19) $NR^c(C=O)O_bR^a$,
20) $O(C=O)O_bC_1$-C_{10} alkyl,
21) $O(C=O)O_bC_3$-C_8 cycloalkyl,
22) $O(C=O)O_b$aryl, and
23) $O(C=O)O_b$-heterocycle,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^z;

R^3 and R^4 are independently selected from: H, C_1-C_6-alkyl and C_1-C_6-perfluoroalkyl, or

R^3 and R^4 are combined to form $-(CH_2)_t-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from O, $S(O)_m$, $-N(R^b)C(O)-$, and $-N(COR^a)-$;

R^5 and R^6 are independently selected from:

1) H,
2) $(C=O)O_bR^a$,
3) C_1-C_{10} alkyl,
4) aryl,
5) C_2-C_{10} alkenyl,
6) C_2-C_{10} alkynyl,
7) heterocyclyl,
8) C_3-C_8 cycloalkyl,
9) SO_2R^a, and
10) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^z, or

R^5 and R^6 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with Q and also optionally substituted with one or more substituents selected from R^z;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1$-C_{10} alkyl,
3) $(C=O)O_bC_3$-C_8 cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) C_1-C_{10} alkyl,
7) aryl,
8) C_2-C_{10} alkenyl,
9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^z, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^z;

R^z is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl,
2) $O_r(C_1$-$C_3)$perfluoroalkyl,
3) $(C_0$-$C_6)$alkylene-$S(O)_mR^a$,
4) oxo,

5) OH,
6) halo,
7) CN,
8) $(C=O)_rO_s(C_2\text{-}C_{10})$alkenyl,
9) $(C=O)_rO_s(C_2\text{-}C_{10})$alkynyl,
10) $(C=O)_rO_s(C_3\text{-}C_6)$cycloalkyl,
11) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-aryl,
12) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
13) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
14) $C(O)R^a$,
15) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
16) C(O)H,
17) $(C_0\text{-}C_6)$alkylene-CO_2H,
18) $C(O)N(R^b)_2$,
19) $S(O)_mR^a$,
20) $S(O)_2N(R^b)_2$,
21) $NR^c(C=O)O_bR^a$,
22) $O(C=O)O_bC_1\text{-}C_{10}$ alkyl,
23) $O(C=O)O_bC_3\text{-}C_8$ cycloalkyl,
24) $O(C=O)O_b$aryl, and
25) $O(C=O)O_b$-heterocycle,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^a is substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_2\text{-}C_6)$alkenyl, substituted or unsubstituted $(C_2\text{-}C_6)$alkynyl, substituted or unsubstituted $(C_3\text{-}C_6)$cycloalkyl, substituted or unsubstituted aryl, $(C_1\text{-}C_6)$perfluoroalkyl, 2,2,2-trifluoroethyl, or substituted or unsubstituted heterocyclyl; and

R^b is H, $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted aryl, substituted or unsubstituted benzyl, substituted or unsubstituted heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C=O)OC_1\text{-}C_6$ alkyl, $(C=O)C_1\text{-}C_6$ alkyl or $S(O)_2R^a$;

R^C is selected from:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_2-C_{10} alkenyl,
5) C_2-C_{10} alkynyl,
6) heterocyclyl,
7) C_3-C_8 cycloalkyl,
8) C_1-C_6 perfluoroalkyl,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^Z, or

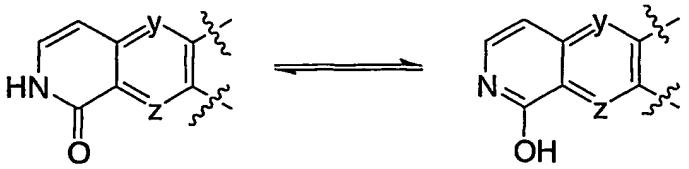
or a pharmaceutically acceptable salt or a stereoisomer thereof.

With respect to compounds of formulas VI through IX the following definitions apply:

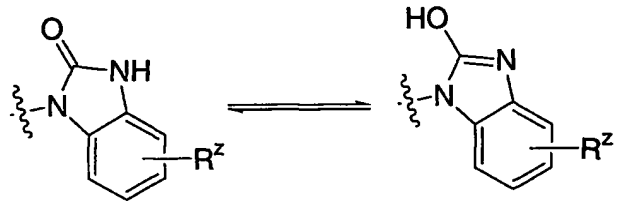
The present invention includes within its scope prodrugs of the compounds of formulae VI-IX above. In general, such prodrugs will be functional derivatives of the compounds of formulae VI-IX which are readily convertible *in vivo* into the required compound of formulae VI-IX. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention.

In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof. The two tautomeric forms of the benzimidazolonyl moiety are also within the scope of the instant ivention.



A B



When any variable (e.g. R^1, R^2, R^z, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrange-

ment. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on. The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on.

"Alkoxy" represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl and cycloalkyl above.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, $CH(CH_3)CH_2CH(CH_3)$Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. Such heteraoaryl moieties for substituent Q include but are not limited to: 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl and 4-isoquinolinyl.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzoimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl,

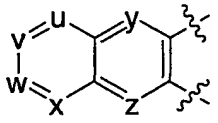
methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

Preferably, heterocycle is selected from 2-azepinone, benzimidazolyl, 2-diazapinone, imidazolyl, 2-imidazolidinone, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinone, 2-pyrimidinone, 2-pyrollidinone, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl.

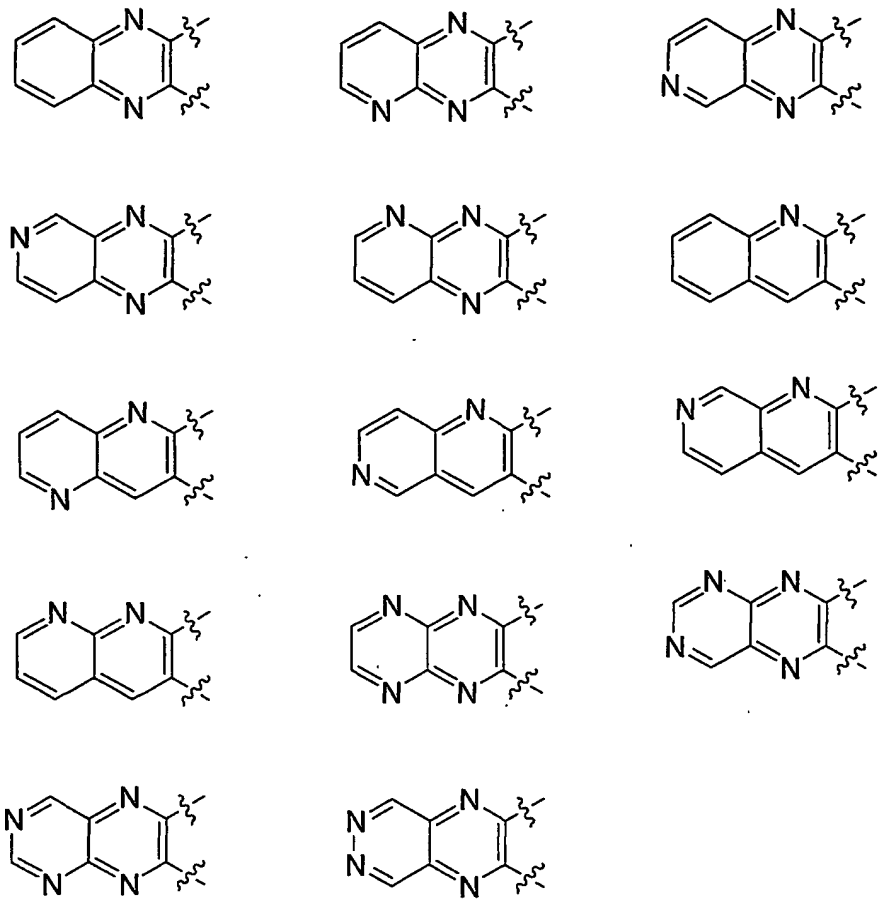
As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

As used herein, unless otherwise specifically defined, substituted alkyl, substituted cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted heteroaryl, substituted arylsulfonyl, substituted heteroaryl-sulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, such substituents are selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6$ alkyl$)_2$, NO_2, CN, $(C_1\text{-}C_6$ alkyl$)O$-, (aryl)O-, -OH, $(C_1\text{-}C_6$ alkyl$)S(O)_m$-, $(C_1\text{-}C_6$ alkyl$)C(O)NH$-, $H_2N\text{-}C(NH)$-, $(C_1\text{-}C_6$ alkyl$)C(O)$-, $(C_1\text{-}C_6$ alkyl$)OC(O)$-, $(C_1\text{-}C_6$ alkyl$)OC(O)NH$-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and $C_1\text{-}C_{20}$ alkyl. For example, a $(C_1\text{-}C_6)$alkyl may be substituted with one, two or three substituents selected from OH, oxo, halogen, alkoxy, dialkylamino, or heterocyclyl, such as morpholinyl, piperidinyl, and so on. In this case, if one substituent is oxo and the other is OH, the following are included in the definition: $-C{=}O)CH_2CH(OH)CH_3$, $-(C{=}O)OH$, $-CH_2(OH)CH_2CH(O)$, and so on.

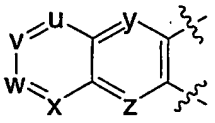
The moiety illustrated in formulas VI and VII by the structure:



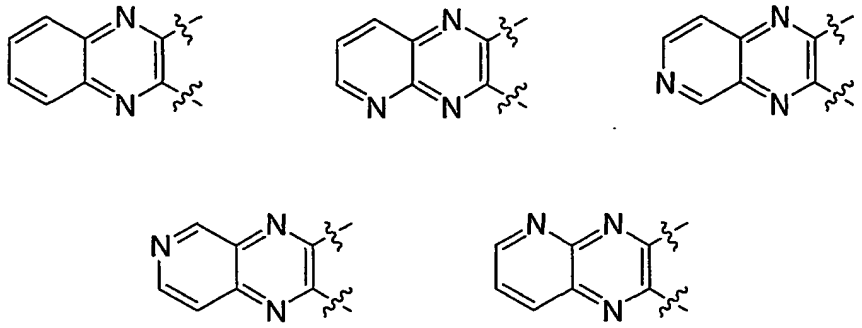
includes the following structures, which are meant to be merely illustrative and not limiting:



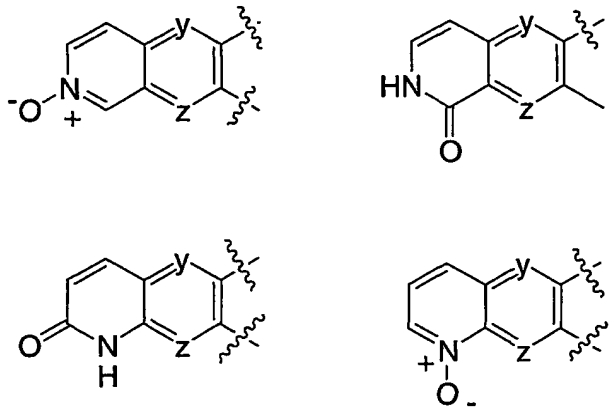
Preferably, the moiety illustrated by the formula:



is selected from:

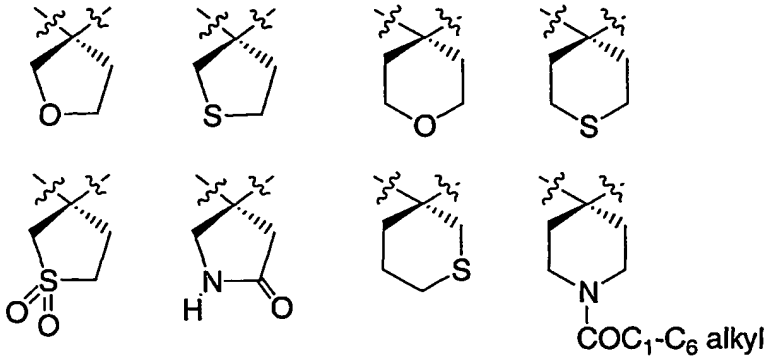


The moieties form when R^1 is oxo include the following structures, which are meant to be merely illustrative and not limiting:

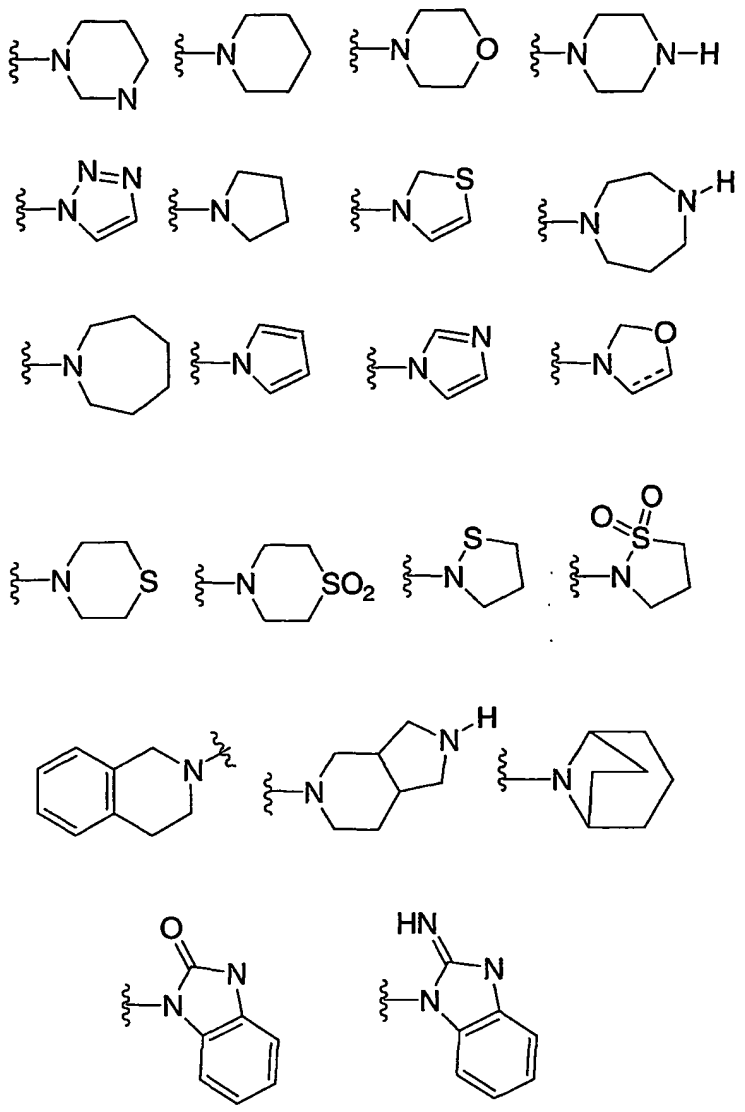


The moiety formed when, in the definition of R^3 and R^4 on the same carbon atom are combined to form $-(CH_2)_t-$ is illustrated by the following:

In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



In certain instances, R^7 and R^8 are defined such that they can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said heterocycle optionally substituted with one or more substituents selected from R^z. Examples of the heterocycles that can thus be formed include, but are not limited to the following, keeping in mind that the heterocycle is optionally substituted with one or more (and preferably one, two or three) substituents chosen from R^z:



Preferably, y and z are N.

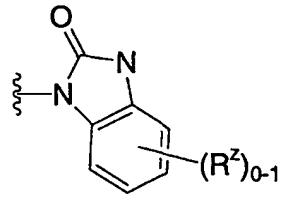
Preferably R^1 is selected from: halogen, -OH, -CN, -NO_2, -CF_3, -OC_1-C_6alkyl, C_1-C_6alkyl, aryl, heterocyclyl, SO_2C_1-C_6 alkyl, -$NR^cSO_2C_1$-C_6 alkyl, -CO_2H, $(C=O)OC_1$-C_6alkyl, -$(C=O)NR^7R^8$, -(C=O)aryl, SO_2aryl and $SO_2NR^7R^8$, optionally substituted with one to three substituents selected from R^z. More preferably, R^1 is -OH, -OC_1-C_6alkyl, -CO_2H, -$(C=O)NR^7R^8$ and C_1-C_6alkyl,.

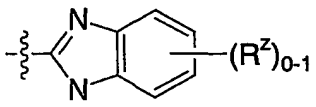
Preferably R^2 is selected from C_1-C_6alkyl, -OH, -OC_1-C_6alkyl, -CF_3, CN and halogen, optionally substituted with one substituent selected from R^z.

Also prefered is the definition of R^3 and R^4 selected from H and $-CH_3$. More prefered R^3 and R^4 are H.

With respect to formula VI, preferably R^5 is selected from H and C_1-C_6 alkyl. More preferably R^5 is H. Preferably R^7 and R^8 are selected from H, C_1-C_6 alkyl and aryl, optionally substituted with one to two substituents selected from R^z. More preferably, R^7 and R^8 are selected from H or C_1-C_6 alkyl.

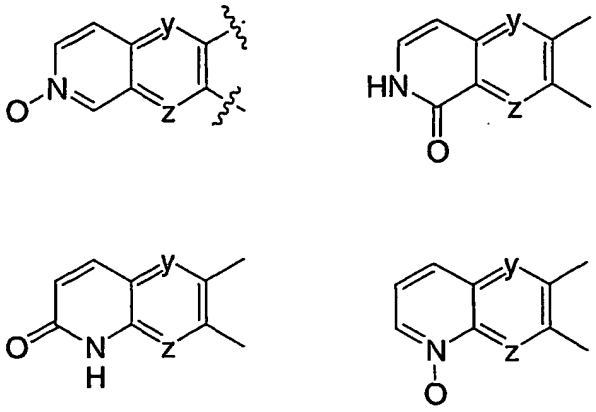
With respect to formula VII, preferably R^5 and R^6 are selected from H, C_1-C_6 alkyl and aryl, optionally substituted with one to two substituents selected from R^z, or R^5 and R^6 together with the nitrogen to which they are attached form a monocyclic or bicyclic heterocycle, optionally substituted with one to two substituents selected from R^z. More preferably, R^5 and R^6 are selected from H or C_1-C_6 alkyl, or R^5 and R^6 together with the nitrogen to which they are attached form a monocyclic or bicyclic heterocycle, optionally substituted with one to two substituents selected from R^z. Preferably, Q is selected from:





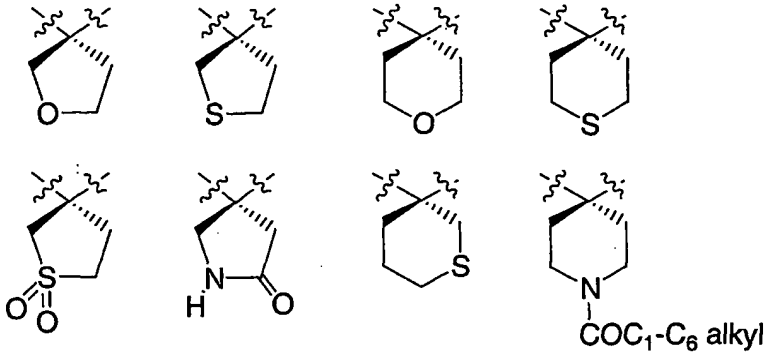
wherein R^z is selected from C_1-C_6 alkyl and halogen.

With respect to the compounds of formula VIII, the moieties formed when R^1 is oxo include the following structure, which are meant to be merely illustrative and not limiting:



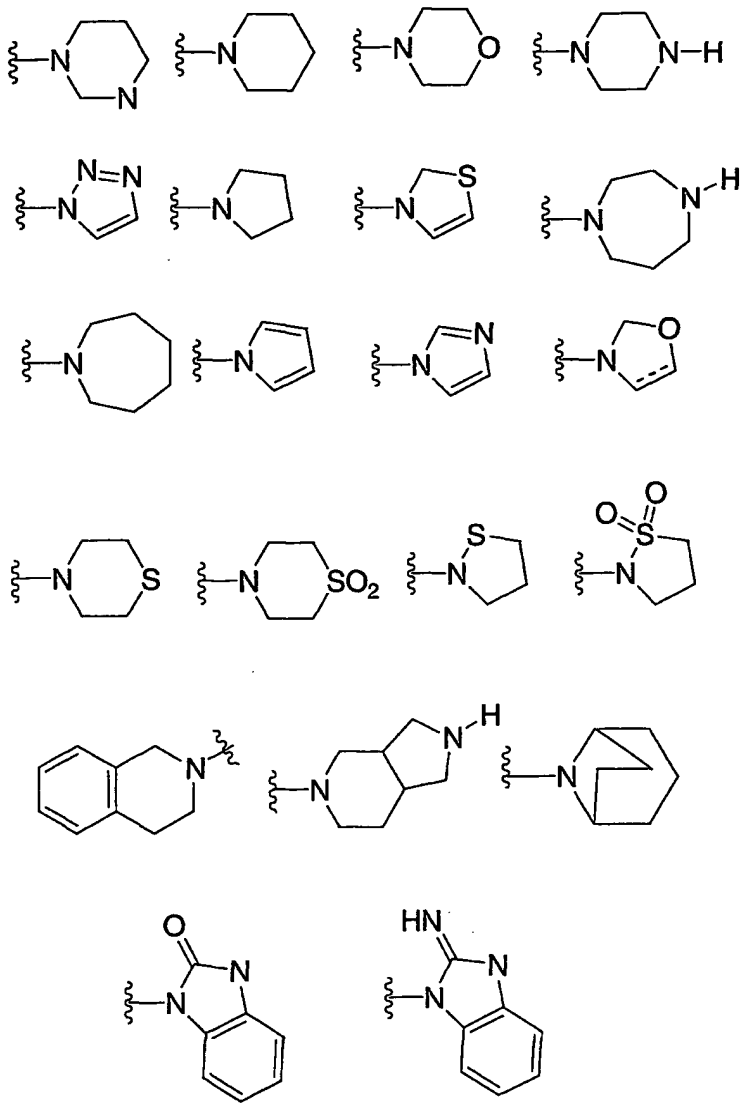
The moiety formed when, in the definition of R^3 and R^4 on the same carbon atom are combined to form $-(CH_2)_t-$ is illustrated by the following:

In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



In certain instances, R^5 and R^6 or R^7 and R^8 are defined such that they can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said heterocycle optionally substituted with one or more substituents selected from R^z. Examples of the heterocycles that can thus be formed

include, but are not limited to the following, keeping in mind that the heterocycle is optionally substituted with one or more (and preferably one, two or three) substituents chosen from R^z:



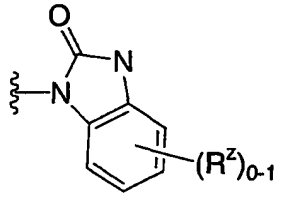
Preferably R^1 is selected from: -OH, -OC_1-C_6alkyl, C_1-C_6alkyl, aryl, heterocyclyl, SO_2C_1-C_6 alkyl, -CO_2H, (C=O)OC_1-C_6alkyl, (C=O)NR^7R^8, SO_2aryl and $SO_2NR^7R^8$, optionally substituted with one to three substituents selected from R^z. More preferably, R^1 is selected from:-OH, -OC_1-C_6alkyl and C_1-C_6alkyl.

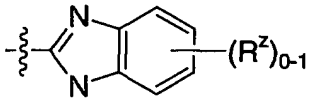
Preferably R^2 is selected from C_1-C_6alkyl, -OH, -OC_1-C_6alkyl, -CF_3, CN and halogen, optionally substituted with one substituent selected from R^z.

Also prefered is the definition of R^3 and R^4 selected from H and -CH_3. More prefered R^3 and R^4 are H.

Preferably R^7 and R^8 are selected from H, C_1-C_6 alkyl and aryl, optionally substituted with one to two substituents selected from R^z. More preferably, R^7 and R^8 are selected from H or C_1-C_6 alkyl.

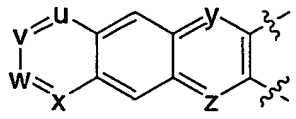
Preferably, Q is selected from:



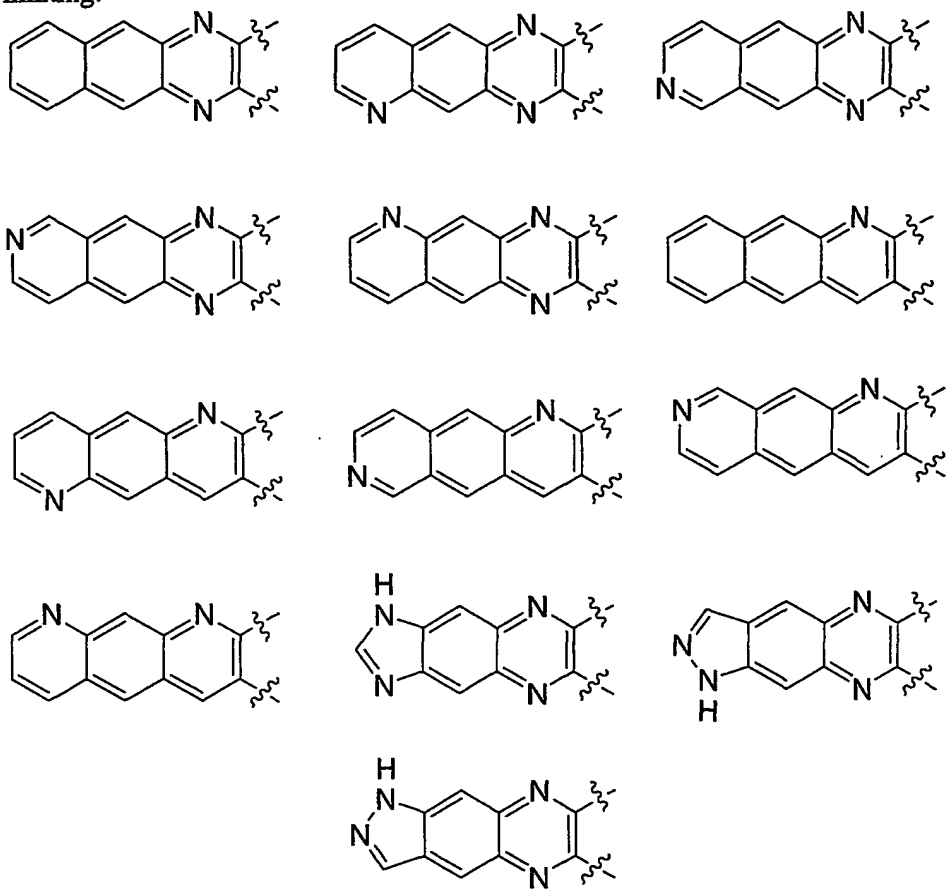


wherein R^z is selected from C_1-C_6 alkyl and halogen.

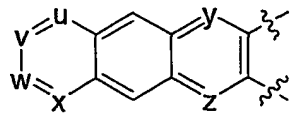
With respect to the compounds of the formula IX, the moiety illustrated by the formula:



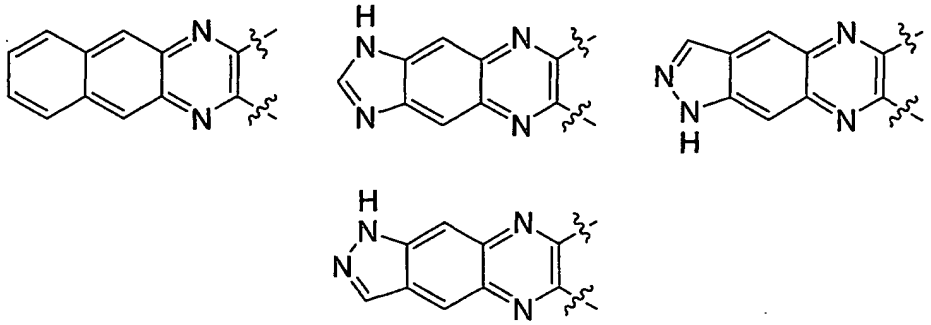
includes the following structures, which are meant to be merely illustrative and not limiting:



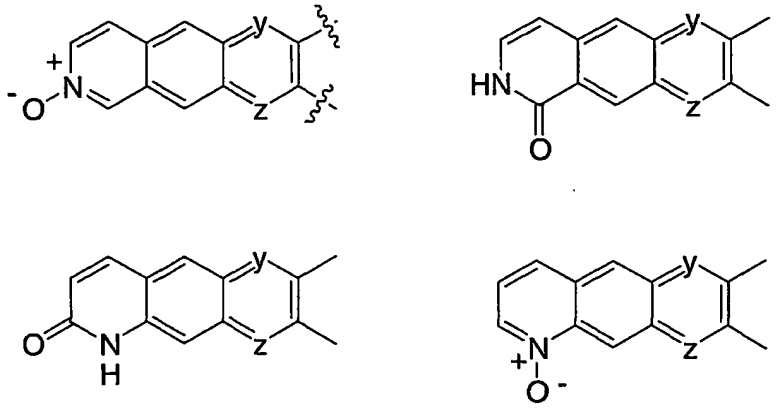
Preferably, the moiety illustrated by the formula:



is selected from:

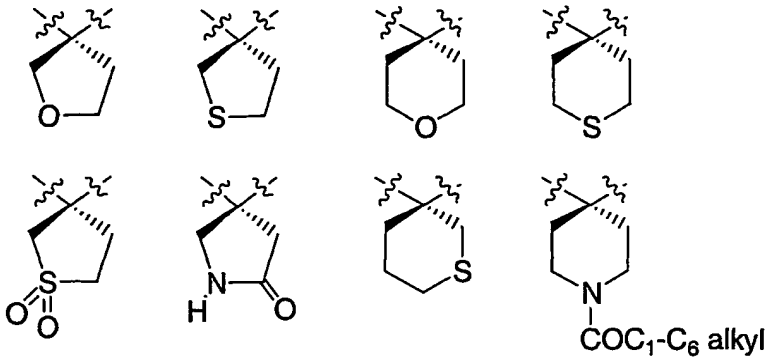


The moieties formed when R^1 is oxo include the following structures, which are meant to be merely illustrative and not limiting:

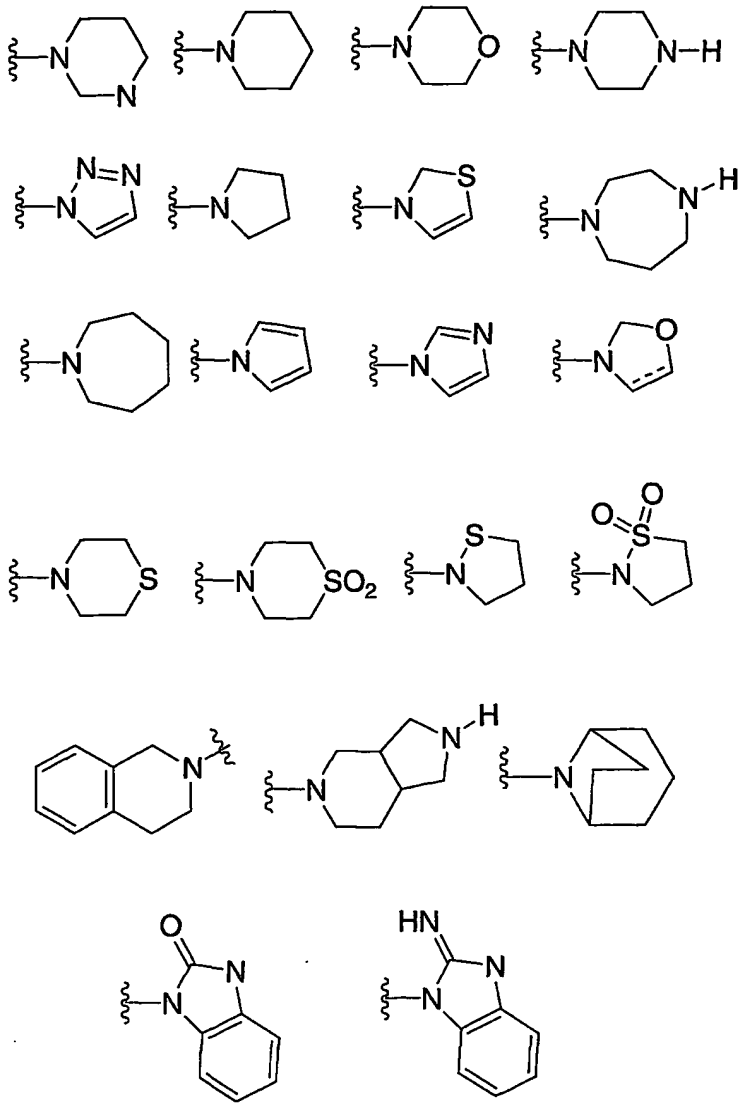


The moiety formed when, in the definition of R^3 and R^4 on the same carbon atom are combined to form $-(CH_2)_t-$ is illustrated by the following:

In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



In certain instances, R^5 and R^6 or R^7 and R^8 are defined such that they can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said heterocycle optionally substituted with one or more substituents selected from R^z. Examples of the heterocycles that can thus be formed include, but are not limited to the following, keeping in mind that the heterocycle is optionally substituted with one or more (and preferably one, two or three) substituents chosen from R^z:



Preferably y and z are N.

Preferably, when w is a bond, two of u, v and x are N.

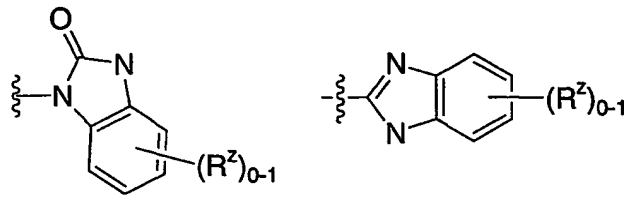
Preferably R^1 is selected from: -OH, -OC_1-C_6alkyl, C_1-C_6alkyl, aryl, heterocyclyl, SO_2C_1-C_6 alkyl, -CO_2H, (C=O)OC_1-C_6alkyl, (C=O)NR^7R^8, SO_2aryl and $SO_2NR^7R^8$, optionally substituted with one to three substituents selected from R^z. More preferably, R^1 is selected from -OH, -OC_1-C_6alkyl and C_1-C_6alkyl,.

Preferably R^2 is selected from C_1-C_6alkyl, -OH, -OC_1-C_6alkyl, -CF_3, CN and halogen, optionally substituted with one substituent selected from R^z.

Also prefered is the definition of R^3 and R^4 selected from H and -CH_3. More prefered R^3 and R^4 are H.

Preferably R^7 and R^8 are selected from H, C_1-C_6 alkyl and aryl, optionally substituted with one to two substituents selected from R^z. More preferably, R^7 and R^8 are selected from H or C_1-C_6 alkyl.

Preferably, Q is selected from:



wherein R^z is selected from C_1-C_6 alkyl and halogen.

Included in the instant invention is the free form of compounds herein disclosed, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the isolated specific compounds exemplified herein are the protonated salts of amine compounds. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the isolated salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formulas I-IX. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

Specific compounds which are inhibitors of one or two of the Akt/PKB isoforms and are therefore useful in the present invention include:

N'-(7-Cyclobutyl-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine;

N'-(7-Cyclobutyl-3-(3,5-difluoro-phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine;

N'-(7-Cyclobutyl-3-(3,4-difluoro-phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine;

N'-(7-Cyclobutyl-3-(4-fluoro-phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine;

N'-(7-Cyclobutyl-3-(3-fluoro-phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine;

2,2,*N*,*N*-tetramethyl-*N*-(3-phenyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)-propane-1,3-diamine;

N'-[3-(4-Methoxy-phenyl)-[1,2,4]triazolo[4,3-*a*]phthalazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine;

6-(2-hydroxyethyl)oxy-3,7-diphenyl-[1,2,4]triazolo[4,3-*b*]pyridazine;

6-(4-hydroxybutyl)oxy-3,7-diphenyl-[1,2,4]triazolo[4,3-*b*]pyridazine;

2-(2-aminoprop-2-ylphenyl)-3-phenylquinazoline;

1-{1-[4-(7-Phenyl-1H-imidazo[4,5-g]quinoxalin-6-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one;

1-{1-[4-(6-Hydroxy-5-isobutyl-3-phenylpyrazin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one;

1-{1-[4-(5-Hydroxy-6-isobutyl-3-phenylpyrazin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one;

1-(1-{4-[5-Hydroxy-6-(1H-indol-3-ylmethyl)-3-phenylpyrazin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one;

1-(1-{4-[6-Hydroxy-5-(1H-indol-3-ylmethyl)-3-phenylpyrazin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one;

1-{1-[4-(3-Phenylquinoxalin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one;

3-(4-{[4-(2-Oxo-2,3-dihydro-1H-benzamidazol-1-yl)piperdin-1-yl]methyl}phenyl)-2-phenylquinaxoline-6-carboxylic acid;

2-(4-{[4-(2-Oxo-2,3-dihydro-1H-benzamidazol-1-yl)piperdin-1-yl]methyl}phenyl)-2-phenylquinaxoline-6-carboxylic acid;

N-[3-(1H-Imidazol-1-yl)propyl]-3-(4-{[4-(2-oxo-2,3-dihydro-1H-benzamidazol-1-yl)piperdin-1-yl]methyl}phenyl)-2-phenylquinaxoline-6-carboxamide;

1-{1-[4-(3-phenylpyrido[3,4-b]pyrazin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one;

1-{1-[4-(2-phenylpyrido[3,4-b]pyrazin-3-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one;

N-[2-(diethylamino)ethyl]-2-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-3-phenylquinoxaline-6-carboxamide;

N-[2-(diethylamino)ethyl]-3-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carboxamide;

4-cyano-N-{(3R)-1-[4-(3-phenylquinoxalin-2-yl)benzyl]pyrrolidin-3-yl}benzamide;

N-{(3R)-1-[4-(3-phenylquinoxalin-2-yl)benzyl]pyrrolidin-3-yl}-1,3-thiazole-5-carboxamide;

2-(4-{[4-(6-amino-9H-purin-9-yl)piperidin-1-yl]methyl}phenyl)-3-phenylquinoxalin-6-amine;

9-{1-[4-(3-phenylpyrido[3,4-b]pyrazin-2-yl)benzyl]piperidin-4-yl}-9H-purin-6-amine;

9-{1-[4-(3-phenylpyrido[2,3-b]pyrazin-2-yl)benzyl]piperidin-4-yl}-9H-purin-6-amine;

2-(4-{[4-(6-amino-9H-purin-9-yl)piperidin-1-yl]methyl}phenyl)-3-phenylquinoxaline-6-carboxylic acid;

1-{1-[4-(3-phenylquinolin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one;

1-(1-{4-[3-phenyl-6-(1H-tetrazol-5-yl)quinoxalin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one;

1-(1-{4-[3-phenyl-7-(1H-tetrazol-5-yl)quinoxalin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one;

9-(1-{4-[3-phenyl-7-(1H-tetrazol-5-yl)quinoxalin-2-yl]benzyl}piperidin-4-yl)-9H-purin-6-amine; and

9-(1-{4-[3-phenyl-6-(1H-tetrazol-5-yl)quinoxalin-2-yl]benzyl}piperidin-4-yl)-9H-purin-6-amine;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

All patents, publications and pending patent applications identified are hereby incorporated by reference.

The compounds used in the present method may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers,

with all possible isomers, including optical isomers, being included in the present invention. Unless otherwise specified, named amino acids are understood to have the natural "L" stereoconfiguration

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

Ac_2O	acetic anhydride;
Boc	t-butoxycarbonyl;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
TFA:	trifluoroacetic acid
AA:	acetic acid
4-Hyp	4-hydroxyproline
Boc/BOC	t-butoxycarbonyl;
Chg	cyclohexylglycine
DMA	dimethylacetamide
DMF	dimethylformamide;
DMSO	dimethyl sulfoxide;
EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride;
EtOAc	ethyl acetate;
EtOH	ethanol;
FAB	Fast atom bombardment;
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole hydrate;
HOPO	2-hydroxypyridine-N-oxide
HPLC	High-performance liquid chromatography;
IPAc	isopropylacetate
MeOH	methanol
RPLC	Reverse Phase Liquid Chromatography
THF	tetrahydrofuran.

DCE	dichloroethane
DCM	dichloromethane
n-Pr	n-propyl
PS-NMM	polystyrene N-methylmorpholine
TFA	trifluoroacetic acid
MP-$CNBH_3$	macroporous cyanoborohydride;
PS-DCC	polystyrene-dicyclohexyl carbodiimide;
PS-DIEA	polystyrene diisopropylethylamine;

Reactions used to generate the compounds which are inhibitors of Akt activity and are therefore useful in the methods of treatment of this invention are shown in the Reaction Schemes 1-10, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R and R^a, as shown in the Reaction Schemes, represent the substituents R^1 and R^2; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments that are subsequently joined by the alkylation reactions described in the Reaction Schemes.

SYNOPSIS OF REACTION SCHEMES 1-10:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. As illustrated in Reaction Scheme 1, a suitably substituted phenylmaleic anhydride i is treated with hydrazine to form the dihydropyridazone dione ii. Subsequent oxidative chlorination and reaction with a suitably substituted benzoic hydrazide provide the 6-chloro triazolo [4,3-*b*]pyridazine iii. This intermediate can then be treated with a variety of alcohols and amines to provide the compound iv.

Reaction Scheme 2 illustrates preparation of compounds useful in the methods of the instant invention having a cycloalkyl substituent at the 7-position. While a cyclobutyl group is illustrated, the sequence of reactions is generally applicable to incorporation of a variety of unsubstituted or substituted cycloalkyl moieties. Thus, 3,6-dichloropyridazine is alkylated via silver catalyzed oxidative decarboxylation with cyclobutyl carboxylic acid to provide the cyclobutyl

dichloropyridazine v, which then undergoes the reactions described above to provide the instant compound vi.

Reaction Scheme 3 illustrates the same reaction sequence used to prepare compounds of the Formula I

Reaction Scheme 4 illustrates an alternative preparation of the instant compounds (*Tetrahedron Letters* 41:781-784 (2000)).

Reaction Scheme 5 illustrates a synthetic method of preparing the compounds of the Formula IV hereinabove.

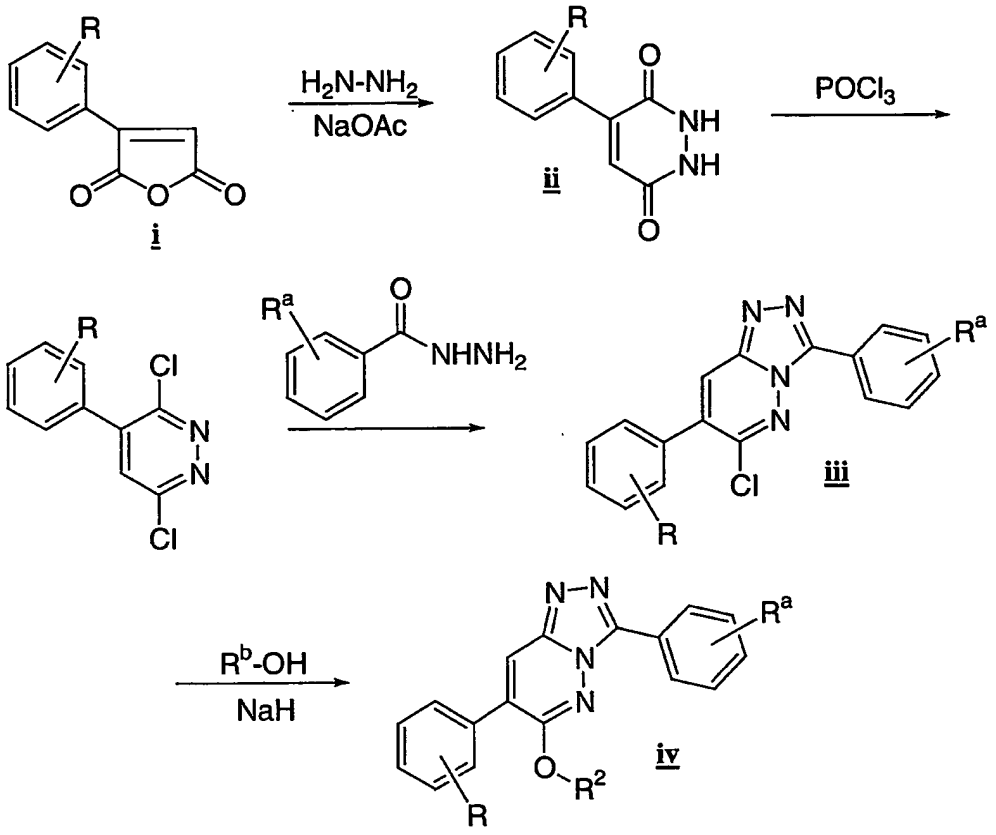
Reaction Scheme 6 illustrates a synthetic method of preparing the compounds of the Formula III hereinabove.

Reaction Scheme 7-8 illustrates a synthetic method of preparing the compounds of the Formula VII hereinabove.

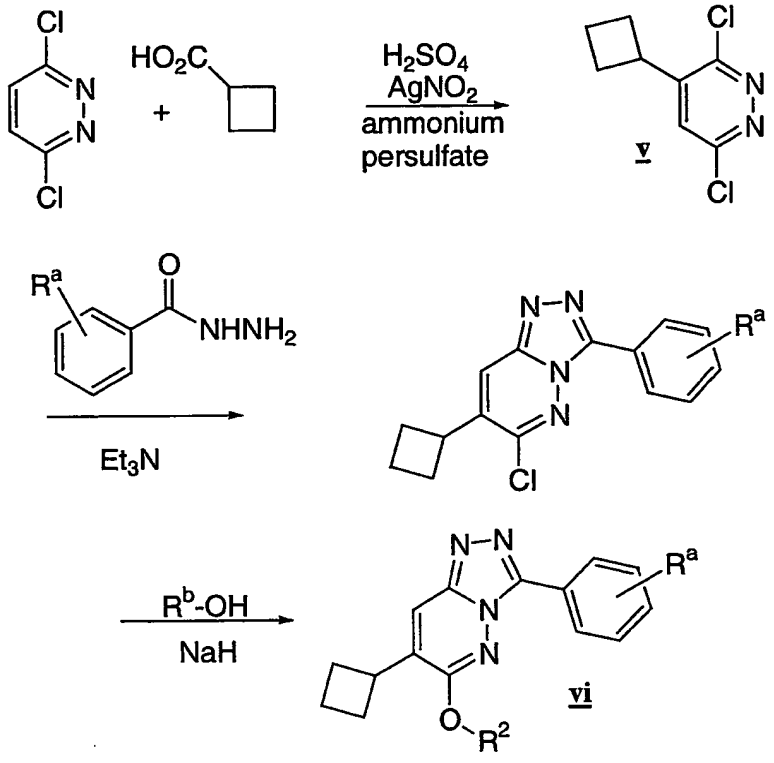
Reaction Schem 9-10 illustrates a synthetic method of preparing the compounds of the Formula IX hereinabove.

5

Reaction Scheme 1

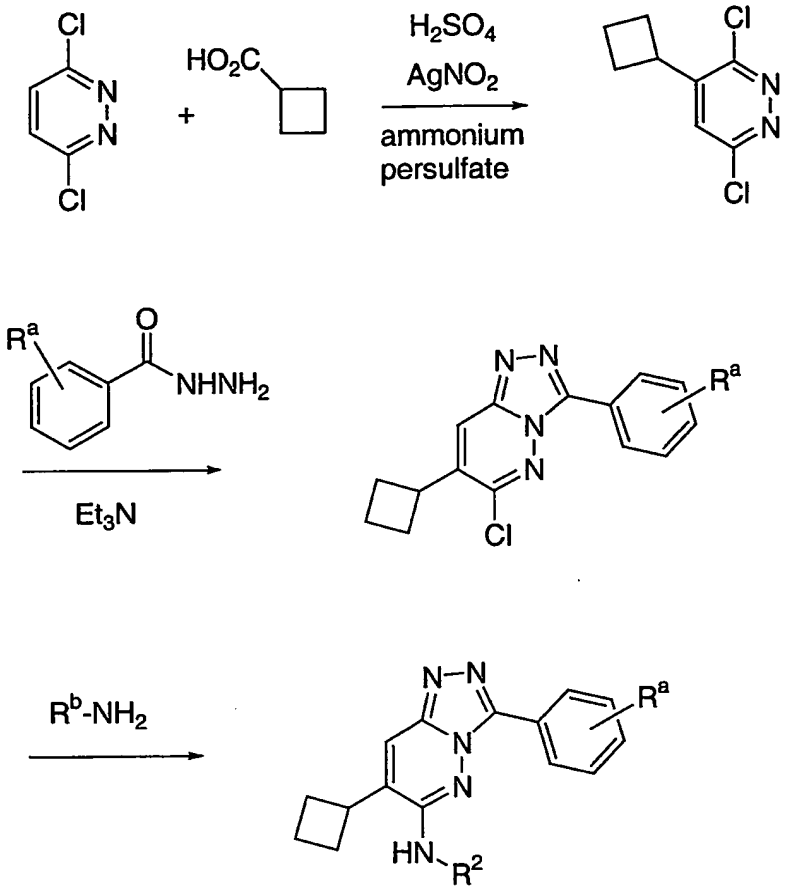


Reaction Scheme 2

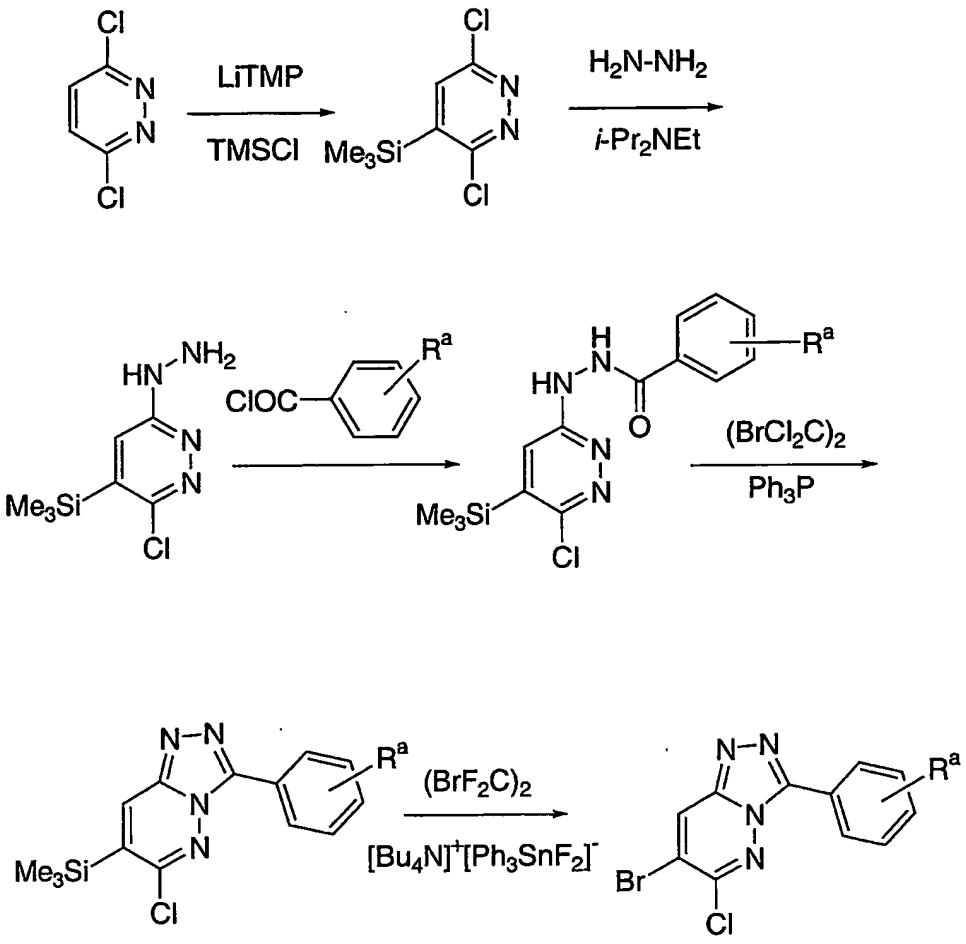


5

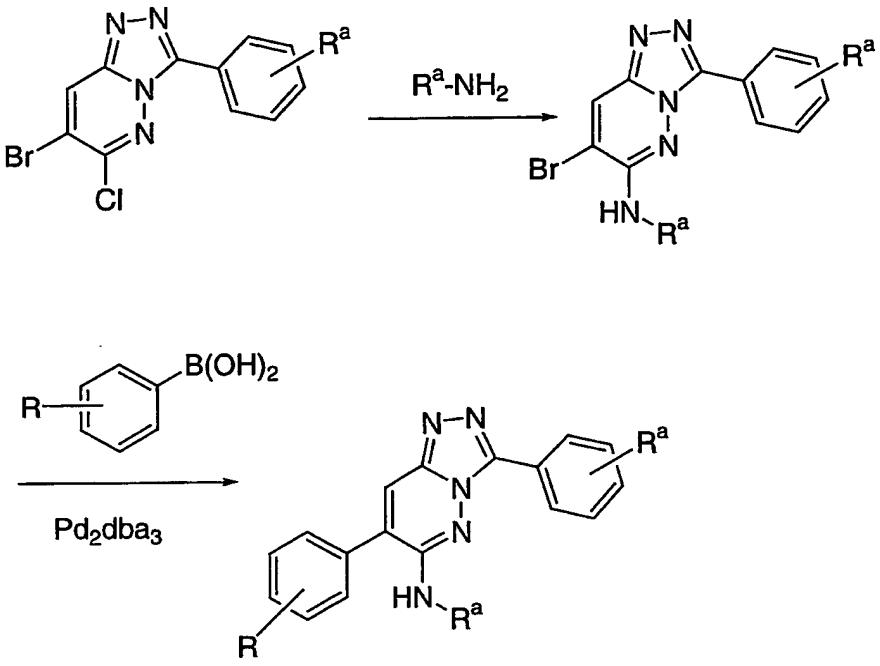
Reaction Scheme 3



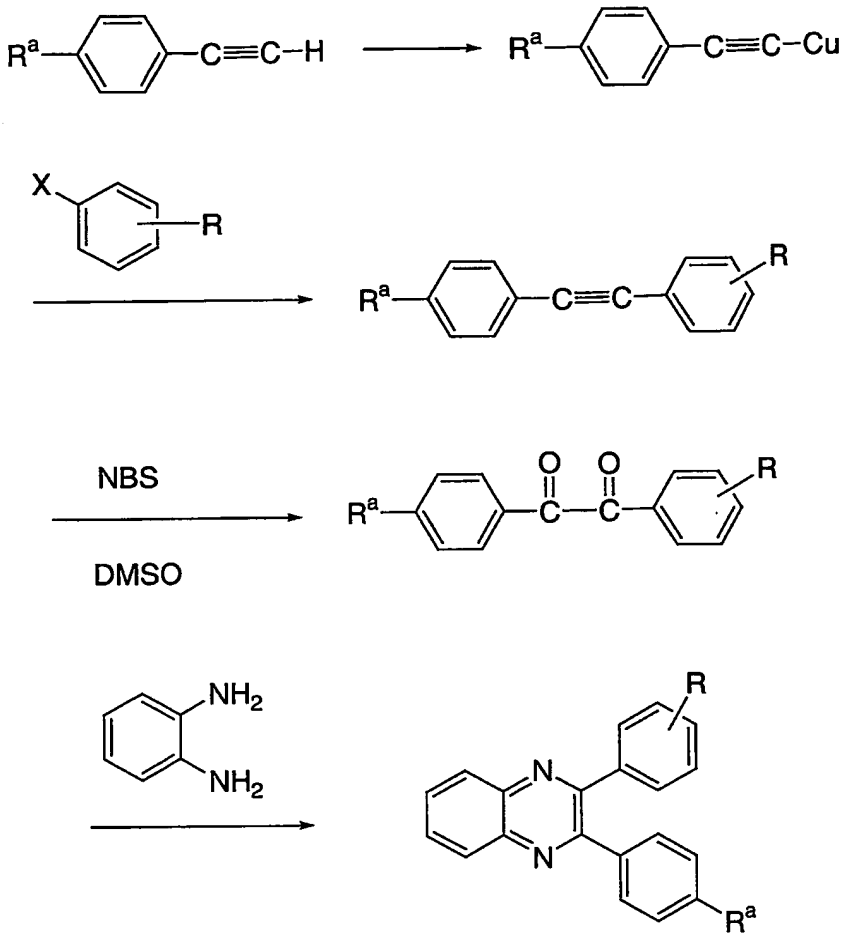
Reaction Scheme 4



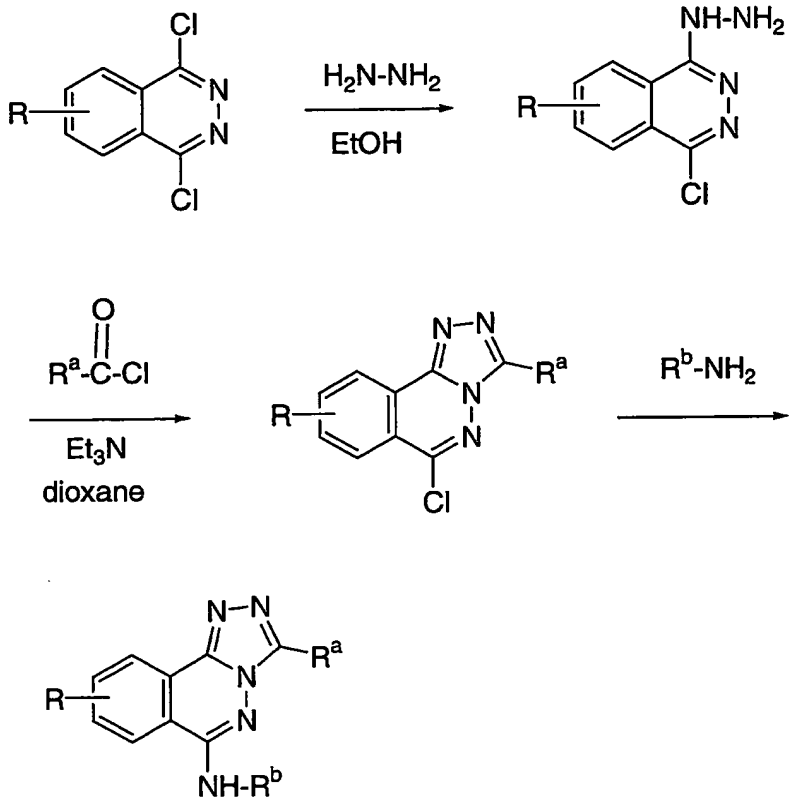
Reaction Scheme 4 (continued)



Reaction Scheme 5

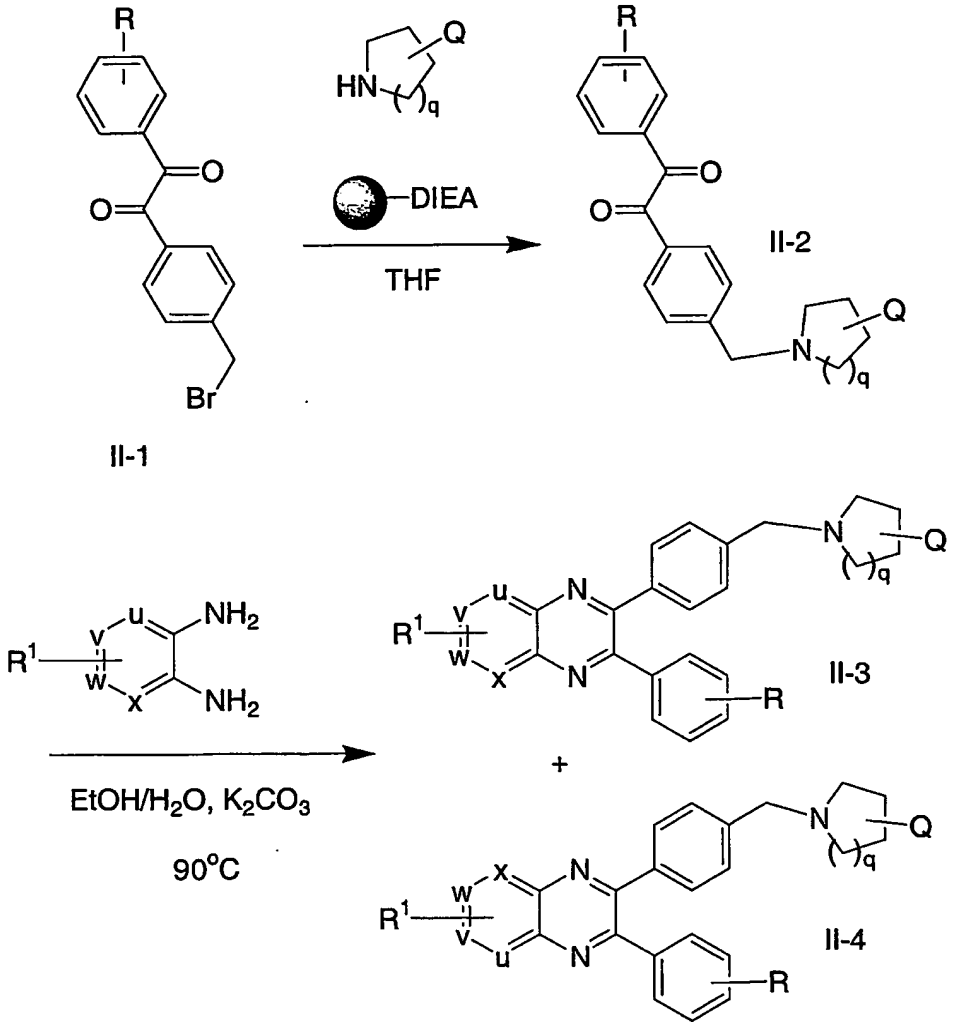


5 Reaction Scheme 6



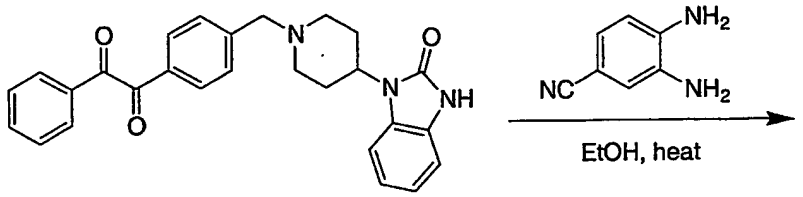
5

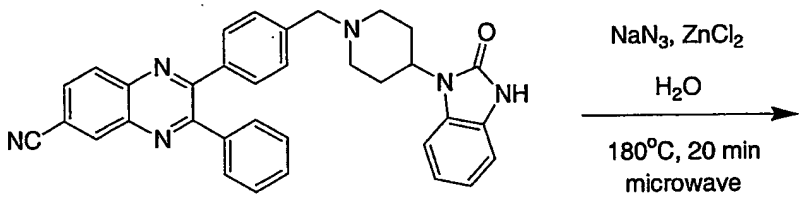
Reaction Scheme 7

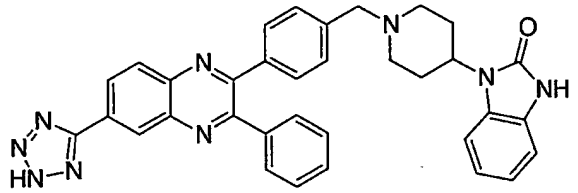


5

Reaction Scheme 8



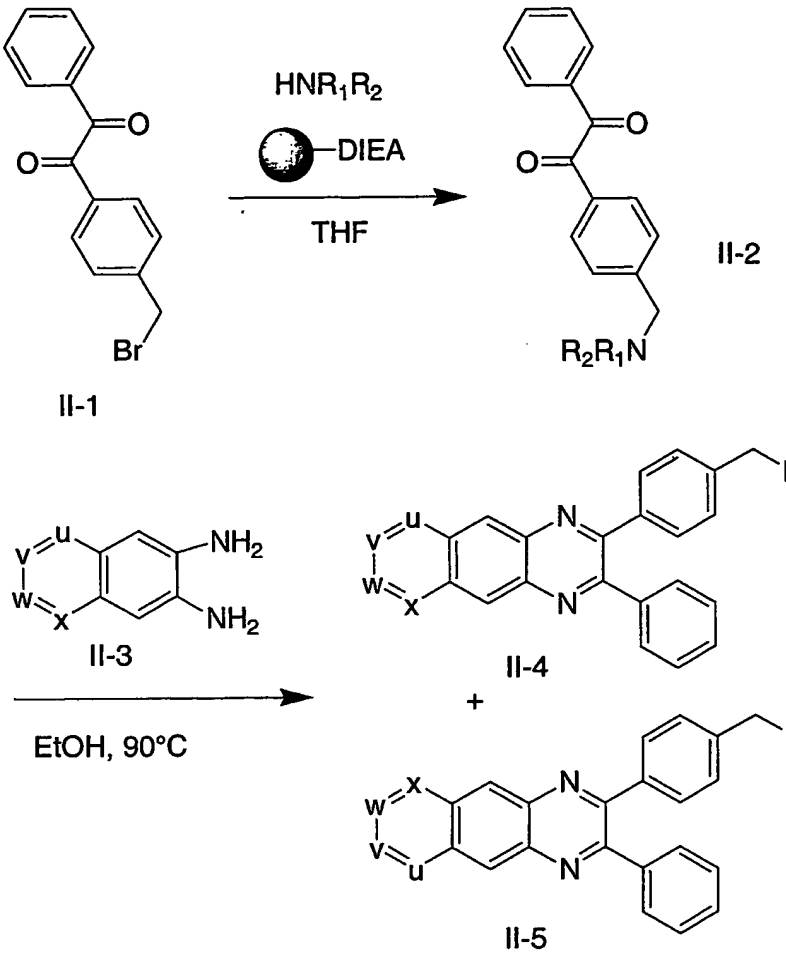




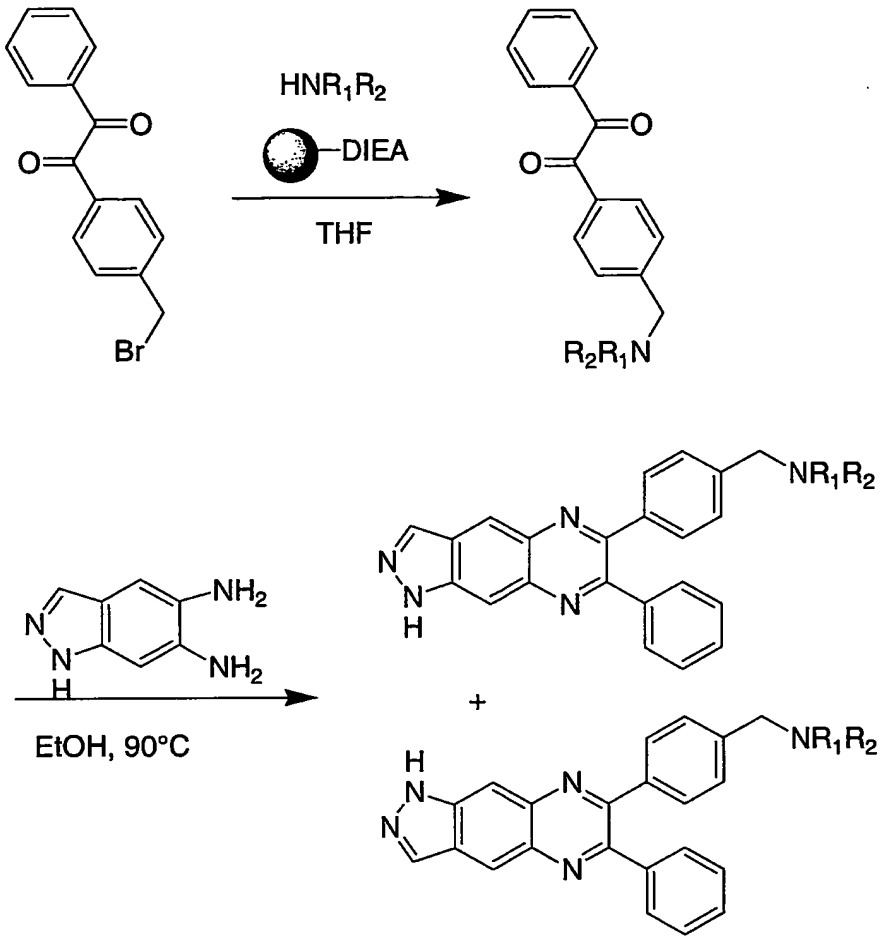
8

5

Reaction Scheme 9



Reaction Scheme 10



EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

N'-(7-Cyclobutyl-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine (Compound 1)

Step 1: 3,6-Dichloro-4-cyclobutylpyridazine

Concentrated sulphuric acid (53.6 ml, 1.0 mol) was added carefully to a stirred suspension of 3,6-dichloropyridazine (50.0 g, 0.34 mol) in water (1.25 l). This mixture was then heated to 70°C (internal temperature) before the addition of cyclobutane carboxylic acid (35.3 ml, 0.37 mol). A solution of silver nitrate (11.4 g, 0.07 mol) in water (20ml) was then added over approximately one minute. This caused the reaction mixture to become milky in appearance. A solution of ammonium persulphate (230 g, 1.0 mol) in water (0.63 l) was then added over 20-30 minutes. The internal temperature rose to approximately 85°C. During the addition the product formed as a sticky precipitate. Upon complete addition the reaction was stirred for an additional 5 minutes, then allowed to cool to room temperature. The mixture was then poured onto ice and basified with concentrated aqueous ammonia, with the addition of more ice as required to keep the temperature below 10°C. The aqueous phase was extracted with dichloromethane (x3). The combined extracts were dried ($MgSO_4$), filtered and evaporated to give the title compound (55.7 g, 82%) as an oil. ^1H nmr ($CDCl_3$) indicated contamination with approximately 5% of the 4,5-dicyclobutyl compound. However, this material was used without further purification. Data for the title compound: ^1H NMR (360 MHz, d_6-DMSO) δ1.79-1.90 (1H, m), 2.00-2.09 (1H, m), 2.18-2.30 (2H, m), 2.33-2.40 (2H, m), 3.63-3.72 (1H, m), 7.95 (1H, s); MS (ES^+) m/e 203 $[MH]^+$, 205 $[MH]^+$, 207 $[MH]^+$.

Step 2: 6-Chloro-7-cyclobutyl-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine

A mixture of 3,6-dichloro-4-cyclobutylpyridazine from above (55.7 g, 0.27 mol), benzoic hydrazide (41.1 g, 0.30 mol) and triethylamine hydrochloride (41.5 g, 0.30 mol) in *p*-xylene (0.4 l) was stirred and heated at reflux under a stream of nitrogen for 24 hours. Upon cooling the volatiles were removed *in vacuo*. The residue was partitioned between dichloromethane and water. The aqueous layer was basified by the addition of solid potassium carbonate. Some dark insoluble material was removed by filtration at this stage. The aqueous phase was further extracted with dichloromethane (x2). The combined extracts were dried ($MgSO_4$), filtered and

evaporated. The residue was purified by chromatography on silica gel eluting with 5%→10%→25% ethyl acetate/dichloromethane to give the title compound, (26.4 g, 34%) as an off-white solid. Data for the title compound: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.90-2.00 (1H, m), 2.12-2.28 (3H, m), 2.48-2.57 (2H, m), 3.69-3.78 (1H, m), 7.49-7.59 (3H, m), 7.97 (1H, s), 8.45-8.48 (2H, m); MS (ES^+) m/e 285 $[MH]^+$, 287 $[MH]^+$.

Step 3: N'-(7-Cyclobutyl-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine

6-Chloro-7-cyclobutyl-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine (100mg) and *N*,*N*,2,2-tetramethyl-1,3-propanediamine (2ml) were heated together in a sealed tube at 70°C for 16 hours. Cooled and water (5ml) added. Precipitate filtered, washed (water, ether) and dried. ^{1}H NMR (250MHz, DMSO) δ 1.20 (6H, s), 2.10 (1H, m), 2.24-2.65 (14H, m), 3.53-3.70 (2H, m), 7.69-7.82 (4H, m), 8.03 (1H, s), 8.70 (2H, m). MS (ES+) MH^+ = 379

EXAMPLE 2

N'-(7-Cyclobutyl-3-(3,5-difluoro-phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine (Compound 2)

The title compound was prepared in an analogous fashion to Example 1, except substituting 3,5-difluorobenzoic hydrazine for the benzoic hydrazine in Step 2. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.07 (6H, s), 1.99 (1H, m), 2.10-2.50 (13H, m), 3.31-3.35 (3H, m), 6.84-6.89 (1H, m), 7.63 (1H, s), 7.90 (1H, vbs), 8.20-8.23 (2H, m). MS (ES+) MH^+ = 415

EXAMPLE 3

N'-(7-Cyclobutyl-3-(3,4-difluoro-phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine (Compound 3)

The title compound was prepared in an analogous fashion to Example 1, except substituting 3,4-difluorobenzoic hydrazine for the benzoic hydrazine in Step 2. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.07 (6H, s), 1.99-2.49 (14H, m), 3.30-3.33 (3H, m), 7.25-7.30 (1H, m), 7.62 (1H, s), 7.87 (1H, vbs), 8.32-8.34 (1H, m), 8.51-8.57 (1H, m). MS (ES+) MH^+ = 415

EXAMPLE 4

N'-(7-Cyclobutyl-3-(4-fluoro-phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine (Compound 4)

The title compound was prepared in an analogous fashion to Example 1, except substituting 4-fluorobenzoic hydrazine for the benzoic hydrazine in Step 2. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.06 (6H, s), 1.98-2.49 (14H, m), 3.31-3.32 (3H, m), 7.18-7.26 (2H, m), 7.61 (1H, s), 7.80 (1H, vbs), 8.55-8.59 (2H, m). MS (ES+) MH^+ = 397

EXAMPLE 5

N'-(7-Cyclobutyl-3-(3-fluoro-phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine (Compound 5)

The title compound was prepared in an analogous fashion to Example 1, except substituting 3-fluorobenzoic hydrazine for the benzoic hydrazine in Step 2. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.07 (6H, s), 1.96-2.50 (14H, m), 3.31-3.35 (3H, m), 7.10-7.15 (1H, m), 7.44-7.50 (1H, m), 7.63 (1H, m) 7.81 (1H, vbs), 8.35-8.42 (2H, m). MS (ES+) MH^+ = 397

EXAMPLE 6

2,2,*N*,*N*-tetramethyl-*N*-(3-phenyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)-propane-1,3-diamine (Compound 6)

Step 1: 1-Chloro-4-hydrazinophthalazine hydrochloride

To a stirred solution of hydrazine hydrate (40ml) in ethanol (120Ml) at 80°C was added 1,4-dichlorophthalazine (20g). This reaction mixture was stirred at 80°C for 0.5 hours, then left to cool and the product was collected by filtration and dried under vacuum to give 1-chloro-4-hydrazinophthalazine hydrochloride (14.6g). ^{1}H NMR (250 MHz, DMSO) δ 4.64 (2H, vbs), 7.2 (1H, vbs), 7.92 (4H, bm).

Step 2: 6-Chloro-3phenyl-1,2,4-triazolo[3,4-a]phthalazine

To a solution of 1-chloro-4-hydrazinophthalazine hydrochloride (10g) in dioxan (220ml) was added triethylamine (7.24ml) and benzoyl chloride (6.04ml).

This mixture was heated at reflux for 8 hours under nitrogen. After cooling the reaction mixture was concentrated under vacuum and the solid obtained was collected by filtration, washed with water and diethyl ether and dried under vacuum, to yield the title compound (12.0g). ^{1}H NMR (250 MHz, DMSO) δ 7.60 (3H, m), 8.00 (1H, t, *J*=8.4Hz), 8.19 (1H, t, *J*=8.4Hz), 8.31 (3H, m), 8.61 (1H, d, *J*=6.3Hz).

Step 3: 2,2,*N*,*N*-tetramethyl-*N*-(3-phenyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)-propane-1,3-diamine

The title compound was prepared as described in Example 1, Step 3, but replacing the 6-Chloro-7-cyclobutyl-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine with the 6-Chloro-3phenyl-1,2,4-triazolo[3,4-a]phthalazine from Step 2. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.13 (6H, s), 2.35 (2H, s), 2.46-2.50 (8H, m), 3.47 (2H, vbs), 7.16-7.27 (2H, m), 7.44-7.86 (5H, m), 8.55-8.57 (2H, m), 8.68 (1H, m). MS (ES+) $MH^+ = 375$

EXAMPLE 7

N'-[3-(4-Methoxy-phenyl)-[1,2,4]triazolo[4,3-*a*]phthalazin-6-yl)-2,2,*N*,*N*-tetramethyl-propane-1,3-diamine (Compound 7)

The title compound was prepared in an analogous fashion to Example 1, except substituting 3-fluorobenzoic hydrazine for the benzoic hydrazine in Step 2. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.13 (6H, s), 2.45 (6H, s), 2.49 (2H, s), 3.45-3.46 (2H, m), 3.90 (3H, s) 7.04-7.07 (2H, m), 7.65-7.70 (2H, m), 7.80-7.84 (1H, m), 8.51 (2H, m), 8.66 (1H, m). MS (ES+) $MH^+ = 405$

EXAMPLE 8

6-(2-Hydroxyethyl)oxy-3,7-diphenyl-[1,2,4]triazolo[4,3-*b*]pyridazine (Compound 8)

Step 1: 4-Phenyl-1,2-dihydropyridazine-3,6-dione

Phenylmaleic anhydride (30 g, 0.17 mol), sodium acetate trihydrate (28 g, 0.21 mol) and hydrazine monohydrate (10 ml, 0.21 mol) were heated together at reflux in 40% acetic acid (600 ml) for 18 hours. The mixture was cooled at 7°C for 2 hours, then filtered. The solid was washed with diethyl ether and dried *in vacuo* to give 11 g (34%) of the title compound: ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.16 (1H, br s), 7.44 (5H, m), 7.80 (2H, br s); MS (ES$^+$) m/e 189 [MH$^+$].

Step 2: 3,6 Dichloro-4-phenylpyridazine

4-Phenyl-1,2-dihydropyridazine-3,6-dinoe (3.4 g, 18 mmol) was heated at reflux in phosphorus oxychloride (70 ml) for 6 hours. The solution was concentrated *in vacuo*, then the residue was dissolved in dichloromethane (100 ml) and was neutralized by the addition of cold 10% aqueous sodium hydrogen carbonate (150 ml). The aqueous phase was washed with dichloromethane (2 x 50 ml), then the combined organic layers were washed with saturated aqueous sodium chloride (50 ml), dried (Na_2SO_4), and concentrated *in vacuo* to yield 3.9 g (97%) of the title compound: ^{1}H NMR (250 MHz,, DMSO- d_6) δ 7.54-7.66 (5H, m) 8.14 (1H, s); MS (ES$^+$) m/e 225/227/229 [MH$^+$].

Step 3: 6-Chloro-3,7-diphenyl-1,2,3-trizolo[4,3-*b*]pyridazine

3,6-Dichloro-4-phenylpyridazine (2.9 g, 13 mmol), benzoic hydrazide (1.9 g, 21 mmol) and triethylammonium chloride (2.0 g, 14 mmol) were heated together at reflux in xylene (150 ml) for three days. More benzoic hydrazide (0.88 g, 6.5 mmol) was added and the mixture was heated as before for another day. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (silica gel, 0-50% EtAOc/CH_2Cl_2) to afford 1.4 g (36%) of the title compound as a solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.55 (8H, m), 8.12 (1H, s), 8.50 (2H, m); MS (ES$^+$) m/e 307/309 [MH$^+$].

Step 4: 6-(2-Hydroxyethyl)oxy-3,7-diphenyl-1,2,3-trizolo[4,3-*b*]pyridazine

Anhydrous DMF (1.5 ml) was added to a test tube containing NaH (13 mg) under nitrogen. Ethylene glycol (2 ml) was added and the mixture stirred at room temperature for 1 hour. The 6-chloro-3,7-diphenyl-1,2,3-trizolo[4,3-*b*]pyridazine (50 mg) (prepared as described in Step 3) was added as a solid and the reaction stirred at room temperature for 30 minutes and then heated at 60°C for 8 hours and then stirred 10 hours at room temperature. The reaction mixture was then poured over 20 ml of hot water, the mixture cooled and the aqueous mixture extracted with ether. The organic phases were combined, washed with water, dried over $MgSO_4$, filtered and concentrated under vacuum to provide the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz at 20°C) δ 8.48 (d, 2H, J = 8.3), 8.04 (d, 1H, J = 0.7), 7.61 (m, 2H), 7.57 (dd, 2H, J = 7.6 and 8.1), 7.52 (m, 4H), 4.62 (dd, 2H, J = 3.9 and 5.1), 4.04 (d, 2H, J = 3.7). LC/MS (ES+) [M+1]= 333.2.

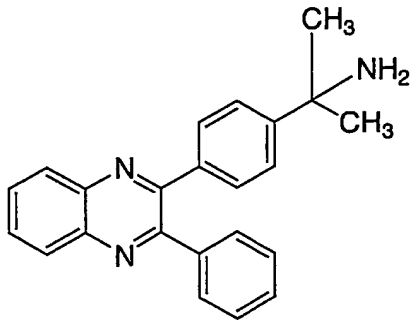
EXAMPLE 9

6-(2-Hydroxybutyl)oxy-3,7-diphenyl-[1,2,4]triazolo[4,3-*b*]pyridazine (Compound 9)

The title compound was prepared by the procedure described in Example 1, but replacing ethylene glycol with 1,4-butanediol in Step 4. ^{1}H NMR ($CDCl_3$, 500 MHz at 20°C) δ 8.52 (dd, 2H, J = 7.8 and 1.5), 8.02 (d, 1H, J = 0.5), 7.58 (m, 4H), 7.51 (m, 4H), 4.53 (t, 2H, J = 6.4), 3.69 (app. t, 2H, J = 5.5), 1.97 (m 2H), 1.72 (m, 2H). LC/MS (ES+) [M+1]= 361.3.

EXAMPLE 10

Preparation of 2-(2-aminoprop-2-ylphenyl)-3-phenylquinazoline (Compound 10)



Step 1: Preparation of Ethyl 4-iodobenzoate

A mixture of 21.0 g of 4-iodobenzoic acid, 100ml of absolute EtOH and 6 ml of concentrated sulfuric acid was refluxed with stirring for 6 days. At the end of this time the reaction mixture was concentrated by boiling and an additional 4 ml of concentrated sulfuric acid added. The mixture was then refluxed for an additional 11 days, after which the mixture was cooled and 50 g of ice and 150 ml Et_2O were added. The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic phases were washed with water, sat. aqueous $NaHCO_3$ and water. The organic phase was then dried over $MgSO_4$ and concentrated under vacuum to provide the title compound as a clear brownish liquid.

Step 2: Preparation of α,α-dimethyl-4-iodobenzyl alcohol

To a cooled (ice/H_2O) solution of 2.76 g of ethyl 4-iodobenzoate (prepared as described in Step 1) in 10 ml of anhyd. Et_2O was added, over a 5 minute period, 26.5ml of 1.52M CH_3MgBr/ Et_2O solution. The mixture was stirred at ice bath temperature for 2.5 hours and then quenched by slow addition of 6 ml of H_2O. The reaction mixture was filtered and the solid residue rinsed with ether. The combined filtrates were dried over $MgSO_4$ and concentrated under vacuum to provide the title compound as a clear yellowish liquid.

Step 3: Preparation of α,α-dimethyl-4-iodo-N-formamido-benzyl amine

19 ml of glacial acetic acid was cooled in an ice bath until a slurry formed. 4.18g of sodium cyanide was added over a 30 minute period. A cooled (ice/H_2O) solution of 10,3 ml conc. sulfuric acid in 95 ml glacial acetic acid was added to the cyanide solution over a 15 min. period. The ice bath was removed and 19.92 g of the α,α-dimethyl-4-iodobenzyl alcohol (prepared as described in Step 2) was added over a 10 minute period. The resulting white suspension was stirred 90 minutes. And left standing overnight at room temperature. The reaction mixture was poured over ice and water and ether added. This mixture was neutralized with solid Na_2CO_3.

Step 4: Preparation of Copper (I) phenylacetylide

To a solution of 10.7 g of phenylacetylene in 500 ml of absolute ethanol was added a solution of 20 g of copper iodide in 250 ml of conc. NH_4OH and 100 ml of water. The solution was stirred 30 minutes and then filtered. The solid that

was collected was washed with water, 95% aq. Ethanol and then ether. The solid was then collected and dried under vacuum to provide the title compound as a bright yellow solid.

Step 5: Preparation of 1-(2-formamidoprop-2-ylphenyl)-2-phenylacetylene

A mixture of 11.83 g of the iodophenyl compound described in Step 3, 6.74 g of Copper (I) phenylacetylide and 165 ml of dry pyridine was stirred at 120•C for 72 hours. The reaction was then allowed to cool and the mixture was poured over approximately 300 g of ice and water with vigorous stirring. The mixture was then extracted with 1:1 benzene:diethylether. The organic solution was washed with 3N hydrochloric acid, dried over $MgSO_4$, filtered and concentrated to provide a solid, that was recrystallized from benzene/cyclohexane to provide the title compound.

Step 6: Preparation of 4-(2-formamidoprop-2-yl)-benzil

1-(2-formamidoprop-2-ylphenyl)-2-phenylacetylene from Step 5 (4.81 g) was dissolved in 30 ml of dried DMSO. N-Bromosuccinamide (NBS) (5.65 g) was added and the reaction stirred at room temperature for 96 hours. At this time 500 mg of NBS was added and the reaction stirred an additional 24 hours. The reaction mixture was then poured over water and the aqueous mixture extracted with benzene. The combined organic phases were washed with water and dried over $MgSO_4$. The organic slurry was then filtered and concentrated *in vacuo* to provide the title compound

Step 7: Preparation of 4-(2-aminoprop-2-yl)-benzil

4-(2-formamidoprop-2-yl)-benzil, prepared as described in Step 6 (6.17 g) was dissolved in 100 ml of glacial acetic acid, 84 ml of water and 6 ml of concentrated HCl. The mixture was stirred at reflux for 3 hours and then the solvent removed under vacuum at 60•C. The residue was converted to the free based form, extracted with organic solvent, washed with water, dried and concentrated to provide the title compound as an oil.

Step 8: Preparation of 2-(2-aminoprop-2-ylphenyl)-3-phenylquinazoline

A mixture of 1.0 g of 4-(2-aminoprop-2-yl)-benzil from Step 7, 0.406 g of o-phenylenediamine, 25 ml of glacial acetic acid and 15 ml of water was refluxed for 4.5 hours. The mixture was then allowed to stand overnight at room temperature.

Most of the solvent was then removed under vacuum and the residue was taken up in 30 ml of water and 50 ml of 6 N aq. NaOH was added. The gum that precipitated was extracted with chloroform. The organic solution was washed with water, dried over $MgSO_4$ and concentrated under vacuum.

The residue was redissolved in chloroform and ethanolic HCl was added, precipitating out the hydrochloride salt. The salt was recrystallized from *i*-PrOH to provide the title compound as the hydrochloride salt - *i*-PrOH solvate (pale yellow plates). Mp 269°C-271°C (melted/resolidified at 250°C).
Anal. Calc. for $C_{23}H_{21}N_3 \cdot HCl \cdot$ *i*-PrOH:

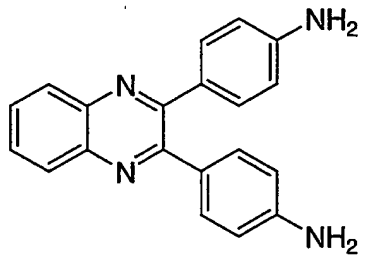
C, 71.62; H, 6.94; N, 9.64.

Found: C, 71.93; H, 6.97; N, 9.72

^1H NMR ($CDCl_3$, 500 MHz at 20°C) δ 9.04 (broad s, 2.4H), 8.10 (d, 1H, $J = 7.8$), 8.02 (d, 1H, $J = 7.8$), 7.72 (dd, 1H, $J = 7.0$ and 8.2), 7.66 (dd, 1H, $J = 7.0$ and 8.2), 7.56 (m, 4H), 7.46 (dd, 2H, $J = 1.2$ and 8.5), 7.31 (m, 3H), 1.81 (s, 6H). LC/MS (ES+) [M+1]= 340.3.

EXAMPLE 11

Preparation of 2,3-bis(4-aminophenyl)-quinoxaline (Compound 11)



Step 1: Preparation of meso (d,l) hydrobenzoin

To a slurry of 97.0 g of benzil in 1 liter of 95% EtOH was added 20 g of sodium borohydride. After stirring 10 minutes, the mixture was diluted with 1 liter of water and the mixture was treated with activated carbon. The mixture was then filtered trough supercel and the filtrate heated and diluted with an additional 2 liters of water until it became slightly cloudy. The mixture was then cooled to 0 to 5°C and the resulting crytals were collected and washed with cold water. The crystals were then dried *in vacuo*.

Step 2: Preparation of 4,4'-dinitrobenzil

150 ml of fuming nitric acid was cooled to -10°C and 25 g of the hydrobenzoin (prepared as described in Step 1) was added slowly portionwise while maintaining the temperature between -10°C to -5°C. The reaction mixture was maintained at 0°C for an additional 2 hours. 70 ml of water was added and the mixture was refluxed for 30 minutes and then poured onto 500 g of cracked ice. The residue was separated from the mixture by decantation and the residue was then boiled with 500 ml of water. The water layer was removed.

The remaining gum was dissolved in boiling acetone and the solution treated with decolorizing carbon and filtered. The filtrated was then cooled to -5°C and the resulting crystals were collected and washed with cold acetone and dried *in vacuo*. An additional crop of crystalline title compound was obtained from recrystallization of the mother liquor residue.

Step 2: Preparation of 4,4'-diaminobenzil

3.8 g of 4,4'-dinitrobenzil was reduced under hydrogen with 3.8g 10% Ru on C in EtOH. The mixture was filtered through Supracel and the filtrate concentrated under vacuum to dryness. The residue was dissolved in 50% denatured ethanol in water, treated with Darco and filtered. The filtrate was cooled to 0°C and the resulting crystals were collected and washed with 50% denatured ethanol in water. The crystals were then dried under a heat lamp to give the title compound as a yellow powder.

Step 3: Preparation of 2,3-bis(4-aminophenyl)-quinoxaline

A mixture of 1.0 g (4.17 mmole) of 4,4'-diaminobenzil and 0.45 g of o-phenylenediamine in 250 ml glacial acetic acid was heated at 50°C for 15 minutes, then stirred for 16 hours at room temperature. The mixture was then heated to 80°C and allowed to cool slowly. The solvent was removed under vacuum and the residue was redissolved in ethanol and that was removed under vacuum.

The solid residue was recrystalized from boiling acetone, and the solid collected. The residue from the mother liquors was recrystalized form 95% EtOH and the resulting crystals combined with the crystals from the acetone crystalization and all were recrystalized from 1:1 abs. EtOH:95% EtOH to provide crystalline material.

The crystals were dried for over 5 hours at 110°C under vacuum to provide the title compound.

Anal. Calc. for $C_{20}H_{16}N_4$:

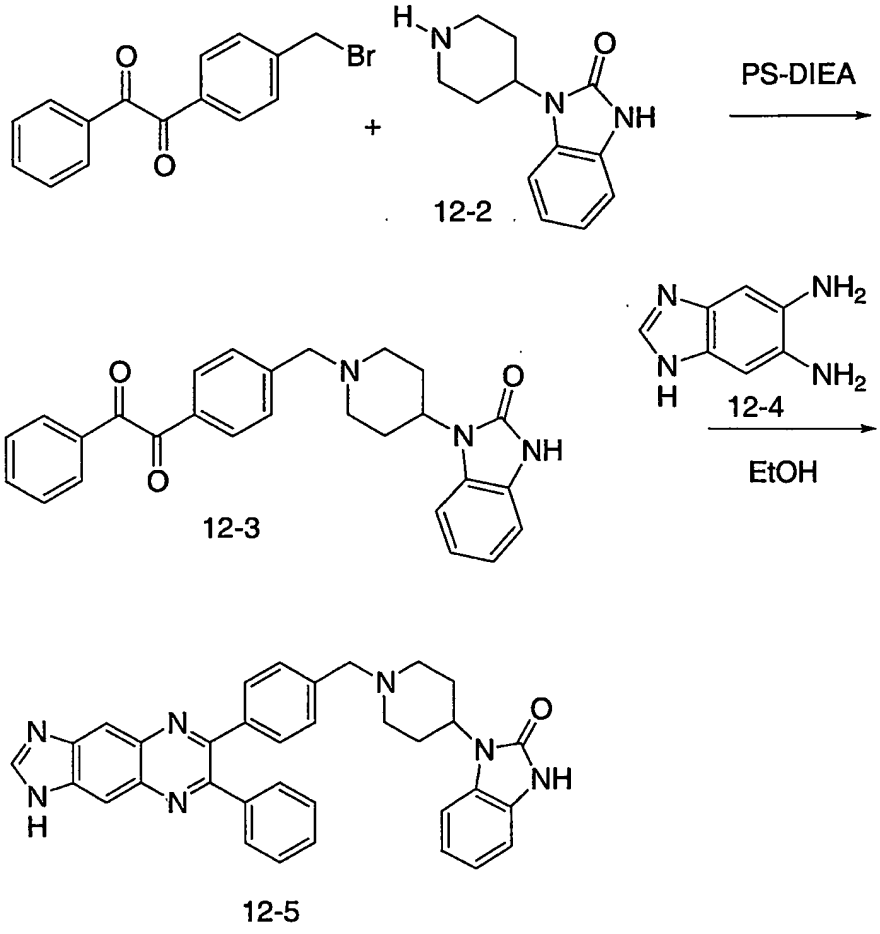
C, 76.90; H, 5.16; N, 17.94.

Found: C, 76.83; H, 4.88; N, 18.16

^{1}H NMR ($CDCl_3$, 500 MHz at 20°C) δ 8.08 (m, 2H), 7.67 (m, 2H), 7.39 (m, 4H), 6.64 (m, 4H), 3.80 (broad s, 4H).

LC/MS (ES+) [M+1]= 313.3.

EXAMPLE 12



Step 1: 1-(4-{[4-(2-Oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (12-3)

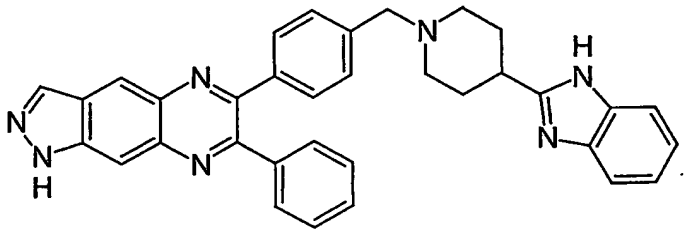
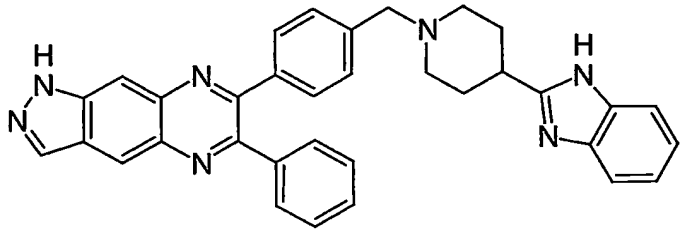
To an 8 mL vial was placed bromomethyl benzil (12-2) (Toronto Research chemicals, 500 mg, 1.65 mmol), 4-(2-keto-1-benzimidazolinyl)piperidine (Aldrich, 358 mg, 1.65 mol), PS-DIEA (887 mg, 3.3 mmol, 3.72 mml/g) and dry THF (6 mL, 0.3 M). The vial was placed on a GlasCol rotator and allowed to rotate for 2 hours. After this time, the contents of the vial were filtered through a 10 mL BioRad tube, washed with THF and concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the TFA salt of (12-3) as a pale yellow solid. Analytical LCMS: single peak (214 nm) at 2.487 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.9 (s, 1H), 8.05 (m, 2H), 7.93 (m, 2H), 7.79 (m, 2H), 7.63 (m, 2H), 7.24 (s, 1H), 6.98 (s, 4H), 4.47 ((s, 2H), 3.5 (m, 2H), 3.2 (m, 3H), 2.61 (q, *J*=11 Hz, 2H), 1.9 (d, *J*=11 Hz, 2H). HRMS, calc'd for $C_{27}H_{26}N_3O_3$ (M+H), 440.1965; found 440.1968.

Step 2: 1-{1-[4-(7-Phenyl-1H-imidazo[4,5-g]quinoxalin-6-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one 12-5

To an 8 mL vial was placed 1-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (12-3) (56 mg, 0.10 mmol), 5,6-diaminobenzimidazole,trihydrochloride (12-4) (25 mg, 0.10 mol) and dissolved in EtOH (2 mL). The vial was placed in a J-KEM heater/shaker block and warmed to 90 degrees for 9 hours. After this time, the vials were cooled and concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford of the TFA salt of (12-5) as a brown solid. Analytical LCMS: single peak (214 nm) at 2.066 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (600 MHz, CD_3OD): δ 9.32 (s, 1H), 8.52 (s, 2H), 7.71 (d, *J*=8.1 Hz, 1H), 7.58 (d, *J*=8.1 Hz, 2H), 7.55 (d, *J*=7.7 Hz, 2H), 7.43 (t, *J*=7.0 Hz, 1H) 7.38 (t, *J*=7.0 Hz, 2H), 7.28 (m, 1H), 7.07 (m, 3H), 4.59 (m, 1H), 4.43 (s, 2H), 3.66 (d, *J*=12.1 Hz, 2H), 3.28 (t, *J*=12.0 Hz, 2H), 2.82 (q, J=11.8 Hz, 2H), 2.08 (d, *J*=13.9 Hz, 2H). HRMS, calc'd for $C_{34}H_{29}N_7O$(M+H), 552.2503; found 552.2503.

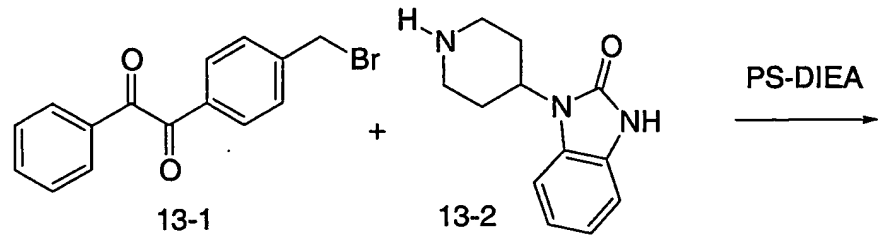
Compounds in Table 1 were synthesized as shown in Example, but substituting the appropriately substituted cyclic amine for compound (12-2) in the example: The TFA salt of the compound shown was isolated by Mass Guided HPLC purification.

Table 1

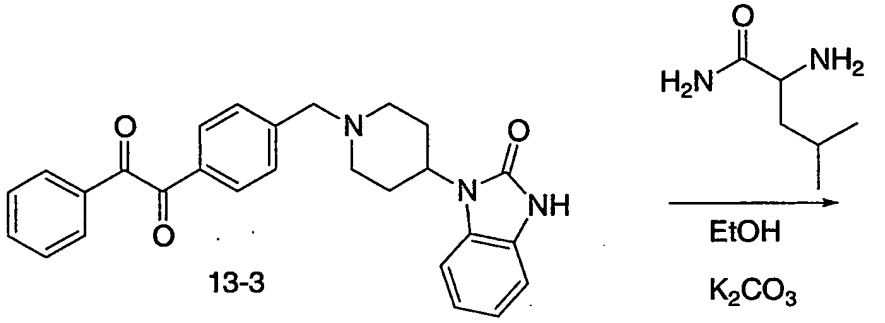
#	Compound	MS M+1
12-6		536.6
12-7		536.6

5

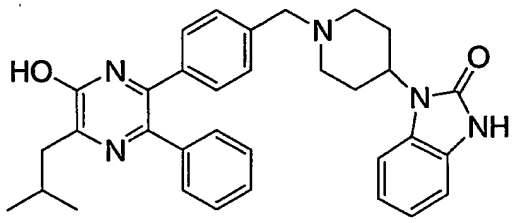
EXAMPLE 13



13-1 13-2

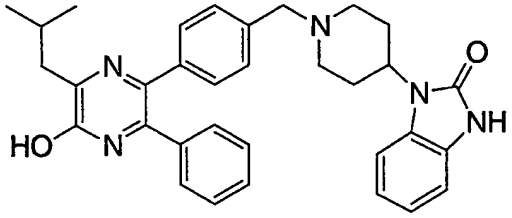


13-3



13-4

\+



13-5

Step 1: 1-(4-{[4-(2-Oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (13-3)

To an 8 mL vial was placed bromomethyl benzil (13-1) (Toronto Research Chemicals, 500 mg, 1.65 mmol), 4-(2-keto-1-benzimidazolinyl)piperidine (13-2) (Aldrich, 358 mg, 1.65 mol), PS-DIEA (887 mg, 3.3 mmol, 3.72 mml/g) and dry THF (6 mL, 0.3 M). The vial was placed on a GlasCol rotator and allowed to rotate for 2 hours. After this time, the contents of the vial were filtered through a 10 mL BioRad tube, washed with THF and concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the TFA salt of (13-3) as a pale yellow solid. Analytical LCMS: single peak (214 nm) at 2.487 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.9 (s, 1H), 8.05 (m, 2H), 7.93 (m, 2H), 7.79 (m, 2H), 7.63 (m, 2H), 7.24 (s, 1H), 6.98 (s, 4H), 4.47 ((s, 2H), 3.5 (m, 2H), 3.2 (m, 3H), 2.61 (q, J=11 Hz, 2H), 1.9 (d, J=11 Hz, 2H). HRMS, calc'd for $C_{27}H_{26}N_3O_3$ (M+H), 440.1965; found 440.1968.

Step 2: 1-{1-[4-(6-Hydroxy-5-isobutyl-3-phenylpyrazin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one 13-4 and 1-{1-[4-(5-Hydroxy-6-isobutyl-3-phenylpyrazin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one (13-5)

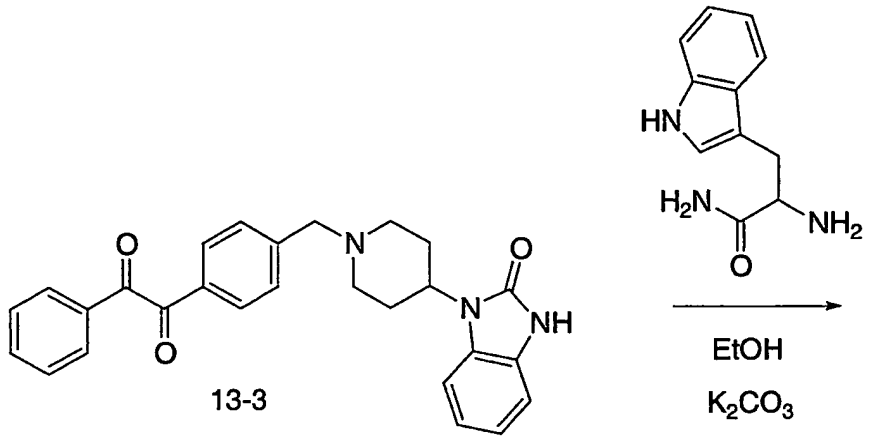
1-(4-{[4-(2-Oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (13-3) (1.661 g, 30 mmol), leucine carboxamide HCl (0.501 g, 3.0 mmol), and K_2CO_3 (0.829 g, 6.0 mmol) were dissolved in 30 mL of EtOH/H_2O (5/1) in a one-necked, 100 ML flask. The mixture solution is heated at 90 °C for 16 hours. After this time, the reaction were cooled and concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the TFA salts of (13-4) and (13-5) as slightly yellow solids.

(13-4): Analytical LCMS: single peak (214 nm) at 2.655min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (500 MHz, CD_3OD): δ 7.54 (d, J=7.9 Hz, 2H), 7.47 (d, J=7.7 Hz, 2H), 7.24 (m, 6H) 7.08 (d, J=2.4 Hz, 3H), 4.57 (m, 1H), 4.40 (s, 2H), 3.63 (d, J=11.5 Hz, 2H), 3.26 (t, J=12.6 Hz, 2H), 2.78 (m, 4H), 2.29 (m,, 2H) 2.09 (d, J=12.8

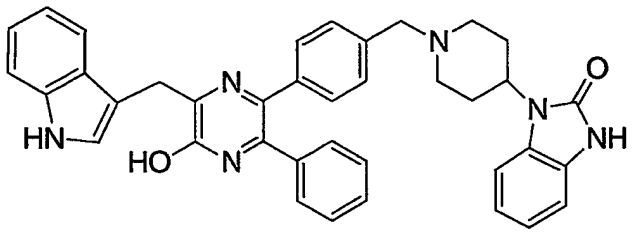
Hz, 2H) 1.02 (d, *J*=6.8 Hz, 6H) . HRMS, calc'd for $C_{33}H_{35}N_5O_2$(M+H),534.2846; found 534.2864.

(13-5): Analytical LCMS: single peak (214 nm) at 2.343 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (500 MHz, CD_3OD): δ 7.39 (m, 9H), 7.24 (m, 1H), 7.07 (m, 3H), 4.54 (m, 1H), 4.33 (s, 2H), 3.63 (d, *J*=12.1 Hz, 2H), 3.21 (t, *J*=12.6 Hz, 2H), 2.77 (q, *J*=12.5, 2H), 2.74 (d, *J*=7.0, 2H) 2.29 (m,, 1H) 2.07 (d, *J*=13.9 Hz, 2H) 1.02 (d, *J*=6.8 Hz, 6H); HRMS, calc'd for $C_{33}H_{35}N_5O2$(M+H),534.2846; found 534.2864. HRMS, calc'd for $C_{33}H_{35}N_5O_2$ (M+H), 534.2846; found 534.2850.

EXAMPLE 14

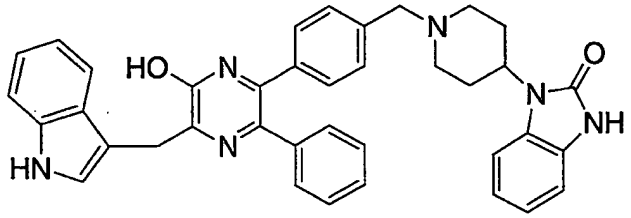


13-3



14-1

\+



14-2

1-(1-{4-[5-Hydroxy-6-(1H-indol-3-ylmethyl)-3-phenylpyrazin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one (14-1) and 1-(1-{4-[6-Hydroxy-5-(1H-indol-3-ylmethyl)-3-phenylpyrazin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one (14-2)

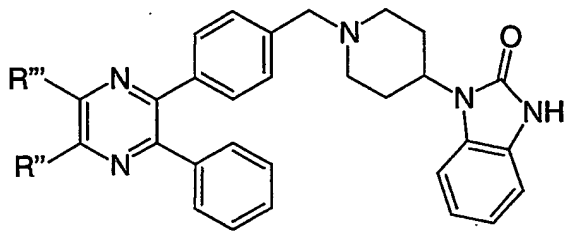
1-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (13-3) (56 mg, 0.1 mmol), L-tryptophan carboxamide (HCl) (24 mg, 0.1 mmol), and K_2CO_3 (28 mg, 0.2 mmol) were dissolved in 2 mL of EtOH/H_2O (5/1) in an 8 mL vial. The mixture solution is heated at 90°C for 16 hours. After this time, the reaction were cooled and concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the TFA salts of (14-1) and (14-2) as brown solids.

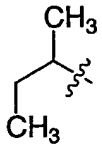
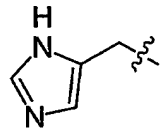
(14-1): Analytical LCMS: single peak (214 nm) at 2.381min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (600 MHz, CD_3OD): δ 7.76 (d, *J*=7.9 Hz 1H), 7.48 (d, *J*=8.6 Hz, 2H), 7.42 (d, *J*=8.6 Hz, 2H) 7.32 (d, *J*=8.0 Hz, 1H), 7.20(m, 6H), 7.07 (m, 5H), 6.99(t, *J*=7.0 Hz, 1H), 4.53 (m, 1H), 4.34 (s, 2H), 4.30 (s, 2H), 3.57 (d, *J*=10.5 Hz, 2H), 3.19 (t, *J*=12.9 Hz, 2H), 2.75 (q, *J*=12.9, 2H), 2.04 (d,, *J*=14.1 2H). HRMS, calc'd for $C_{38}H_{34}N_6O_2$ (M+H),607.2816; found 607.2790.

(14-2): TFA salt as a brown solid. Analytical LCMS: single peak (214 nm) at 2.558min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (500 MHz, CD_3OD): δ 7.76 (d, *J*=7.9 Hz 1H), 7.48 (d, *J*=7.7 Hz, 2H), 7.42 (d, *J*=8.0 Hz, 2H), 7.36 (m, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.23(m, 6H), 7.07 (m, 4H), 6.99(t, *J*=7.5 Hz, 1H), 4.53 (m, 1H), 4.32 (m, 4H), 3.58 (d, *J*=11.0 Hz, 2H), 3.19 (t, *J*=12.9 Hz, 2H), 2.75 (q, *J*=6.7 Hz, 2H), 2.07 (d,, *J*=13.9 Hz, 2H). HRMS, calc'd for $C_{38}H_{34}N_6O_2$ (M+H),607.2816; found 607.2790.

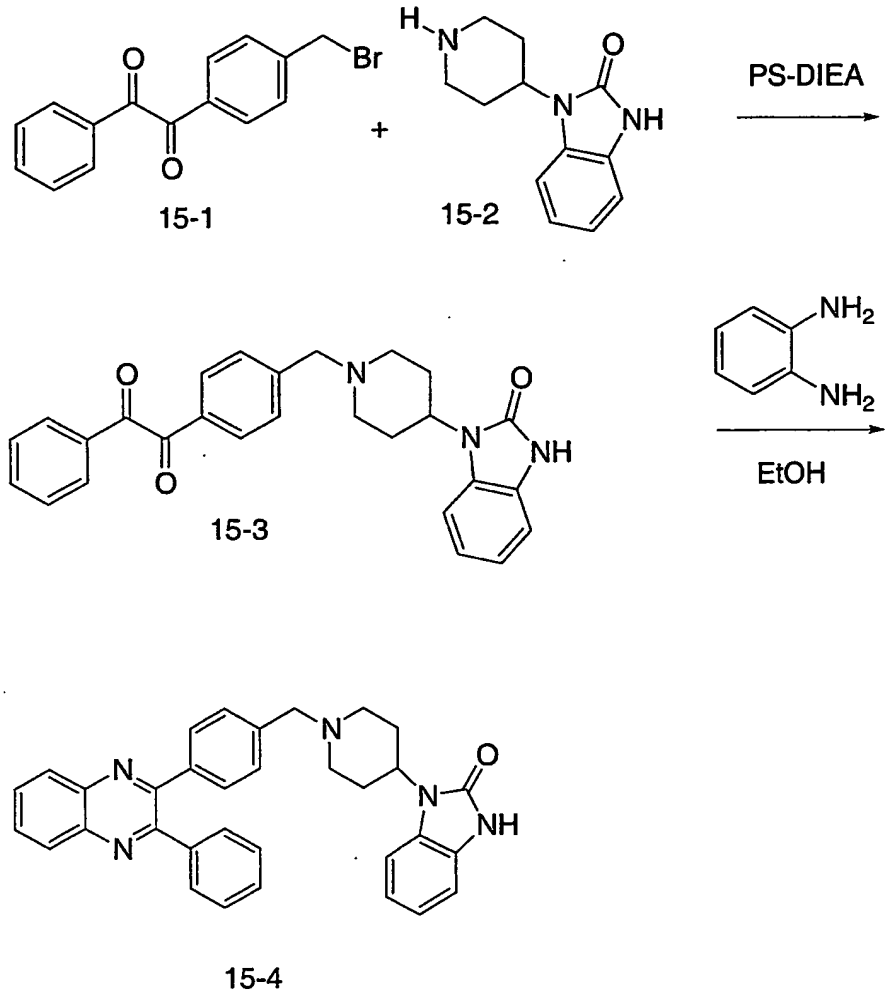
Compounds in Table 2 were synthesized as shown in Examples 13 and 14. The TFA salt of the compound shown was isolated by Mass Guided HPLC purification.

Table 2



#	R''	R'''	MS M+1
13-6	**-CH_2Ph**	**-OH**	568.6
13-7		**-OH**	534.6
13-8	**-OH**		558.6

EXAMPLE 15



Step 1: 1-(4-{[4-(2-Oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (15-3)

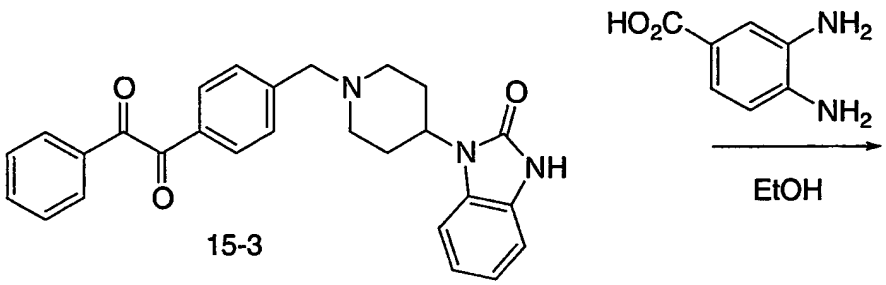
To an 8 mL vial was placed bromomethyl benzil (15-1) (Toronto Research Chemicals, 500 mg, 1.65 mmol), 4-(2-keto-1-benzimidazolinyl)piperidine (15-2) (Aldrich, 358 mg, 1.65 mol), PS-DIEA (887 mg, 3.3 mmol, 3.72 mml/g) and dry THF (6 mL, 0.3 M). The vial was placed on a GlasCol rotator and allowed to rotate for 2 hours. After this time, the contents of the vial were filtered through a 10 mL BioRad tube, washed with THF and concentrated in vaccuo. The crude material was then

purified on an Agilent 1100 series Mass Guided HPLC purification system to afford 775 mg of the TFA salt of (15-3) as a pale yellow solid. Analytical LCMS: single peak (214 nm) at 2.487 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.9 (s, 1H), 8.05 (m, 2H), 7.93 (m, 2H), 7.79 (m, 2H), 7.63 (m, 2H), 7.24 (s, 1H), 6.98 (s, 4H), 4.47 ((s, 2H), 3.5 (m, 2H), 3.2 (m, 3H), 2.61 (q, J=11 Hz, 2H), 1.9 (d, J=11 Hz, 2H). HRMS, calc'd for $C_{27}H_{26}N_3O_3$ (M+H), 440.1965; found 440.1968.

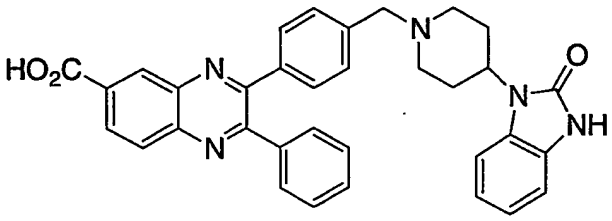
Step 2: 1-{1-[4-(3-Phenylquinoxalin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one (15-4)

To an 8 mL vial was placed 1-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (15-3) (88 mg, 0.16 mmol), 1,2-diaminobenzene (17 mg, 0.16 mol) and dissolved in EtOH (3 mL). The vial was placed in a J-KEM heater/shaker block and warmed to 90 degrees for 9 hours. After this time, the vials were cooled and concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford 80 mg of the TFA salt of (15-4) as a brown solid. Analytical LCMS: single peak (214 nm) at 2.625 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.9 (s, 1H), 8.18 (m, 2H), 7.92 (m, 2H), 7.6 (m, 2H), 7.52 (m, 4H), 7.4 (m, 3H), 7.28 (m, 1H), 7.0 (s, 3H), 4.50 (m, 1H), 4.4 (s, 2H), 3.5 (d, J=12 Hz, 2H), 3.2 (t, J=12 Hz, 2H), 2.6 (q, J=11.8 Hz, 2H), 1.94 (d, J=12 Hz, 2H). HRMS, calc'd for $C_{33}H_{30}N_5O$(M+H), 512.2445; found 512.2443.

EXAMPLE 16

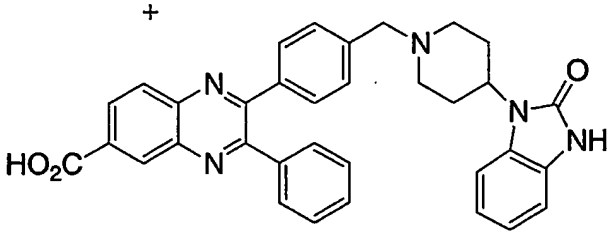


15-3



16-1

+



16-2

3-(4-{[4-(2-Oxo-2,3-dihydro-1H-benzamidazol-1-yl)piperdin-1-yl]methyl}phenyl)-2-phenylquinaxoline-6-carboxylic acid (16-1) and
2-(4-{[4-(2-Oxo-2,3-dihydro-1H-benzamidazol-1-yl)piperdin-1-yl]methyl}phenyl)-2-phenylquinaxoline-6-carboxylic acid (16-2)

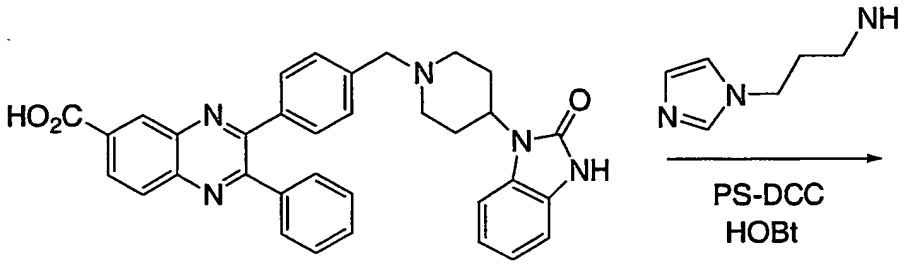
To an 8 mL vial was placed 1-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (15-3) (500 mg, 1.1 mmol), 4-carboxy-1,2-diaminobenzene (170 mg, 1.1 mol) and dissolved in EtOH (10 mL). The vial was placed in a J-KEM heater/shaker block and warmed to 90 degrees for 9 hours. After this time, the vials were cooled and concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the TFA salt as a white solid. This protocol

afforded a 1:1 mixture of regioisomers (16-1) and (16-2) which were separated by prep HPLC.

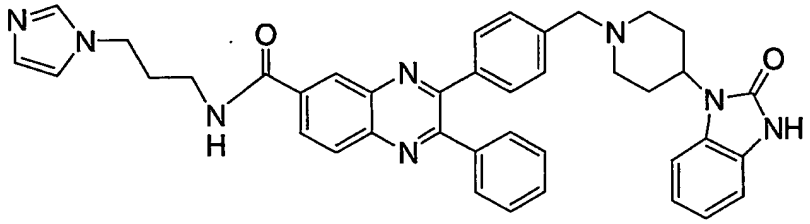
(16-1): Analytical LCMS: single peak (214 nm) at 2.430 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^1H NMR for 2-1 (400 MHz, DMSO-d_6): δ 13.1 (s, 1H), 10.8 (s, 1H), 8.66 (s, 1H), 8.32 (m, 1H), 8.23 (m, 1H), 7.52 (m, 2H), 7.49 (m, 2H), 7.42 (m, 1H), 7.38 (m, 4H), 7.24 (m, 1H), 6.97 (s, 3H), 4.17 (m, 1H), 3.61 (s, 2H), 2.97 (d, J=11.4 Hz, 2H), 2.38 (q, J=10 Hz, 2H), 2.17 (t, J=11.4 Hz, 2H), 1.66 (d, J=10 Hz, 2H). HRMS calc'd for $C_{34}H_{30}N_5O_3$ (M+H), 556.2343; found 556.2352.

(16-2): Analytical LCMS: single peak (214 nm) at 2.620 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^1H NMR for 2-1 (400 MHz, DMSO-d_6): δ 12.9 (s, 1H), 10.6 (s, 1H), 8.60 (s, 1H), 8.30 (m, 1H), 8.27 (m, 1H), 7.55 (m, 2H), 7.49 (m, 2H), 7.42 (m, 1H), 7.38 (m, 4H), 7.24 (m, 1H), 6.97 (s, 3H), 4.17 (m, 1H), 3.61 (s, 2H), 2.97 (d, J=11.4 Hz, 2H), 2.38 (q, J=10 Hz, 2H), 2.17 (t, J=11.4 Hz, 2H), 1.66 (d, J=10 Hz, 2H). HRMS calc'd for $C_{34}H_{30}N_5O_3$ (M+H), 556.2343; found 556.2350.

EXAMPLE 17



16-1



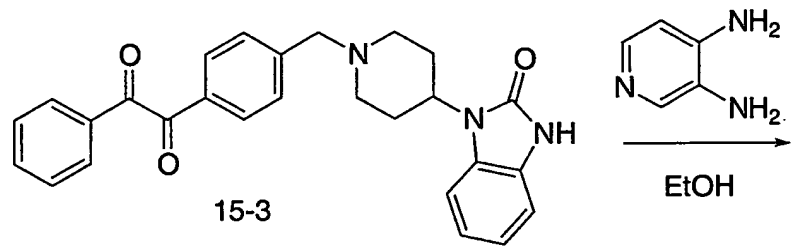
17-1

N-[3-(1H-Imidazol-1-yl)propyl]-3-(4-{[4-(2-oxo-2,3-dihydro-1H-benzamidazol-1-yl)piperdin-1-yl]methyl}phenyl)-2-phenylquinaxoline-6-carboxamide (17-1)

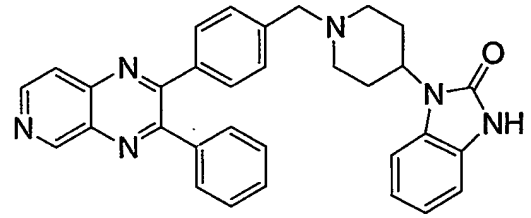
To an 8 mL vial was placed 3-(4-{[4-(2-oxo-2,3-dihydro-1H-benzamidazol-1-yl)piperdin-1-yl]methyl}phenyl)-2-phenylquinaxoline-6-carboxylic acid (16-1) (35 mg, 0.08 mol), 3-imidazoylpropylamine (10 µL, 0.08 mol), PS-DCC (110 mg, 0.15 mmol, 1.38 mmol/g), HOBt (15 mg, 0.11 mmol) and DCM (4 mL). The vial was placed on a GlasCol rotator and allowed to rotate overnight. In the morning, MP-carbonate (90 mg, 0.32 mmol, 3.38 mmol/g) was added, and the vial allowed to rotate for another 3 hours. After this time, the vial's contents were filtered through a BioRad tube, washed with DCM and concentrated. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the bis TFA salt of (17-1) as a brown solid. Analytical LCMS: single peak (214 nm) at 2.090 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.9 (s, 1H), 9.1 (s, 1H), 9.0 (t, J=4.8 Hz, 1H), 8.71 (s, 1H), 8.29 (s, 2H), 7.84 (s, 1H), 7.69 (2, 1H), 7.55 (m, 7H), 7.3 (s, 1H), 7.0 (s, 3H), 4.51 (m, 1H),

4.39 (s, 2H), 4.31 (t, *J*=6.8 Hz, 2H), 3.47 (m, 2H), 3.19 (m, 2H), 2.66 (q, *J*=11.2 Hz, 2H), 2.16 (quint, *J*=6.8 Hz, 2H), 1.94 (d, *J*=12.4 Hz, 2H). HRMS calc'd for $C_{40}H_{39}N_8O_2$ (M+H), 663.3190; found 663.3191.

EXAMPLE 18

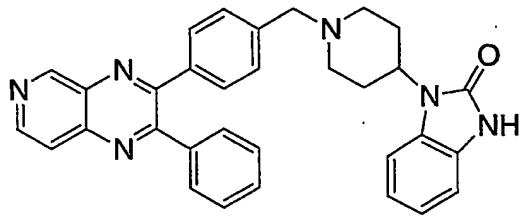


15-3



18-1

+



18-2

1-{1-[4-(3-phenylpyrido[3,4-b]pyrazin-2-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one (18-1) and 1-{1-[4-(2-phenylpyrido[3,4-b]pyrazin-3-yl)benzyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one (18-2)

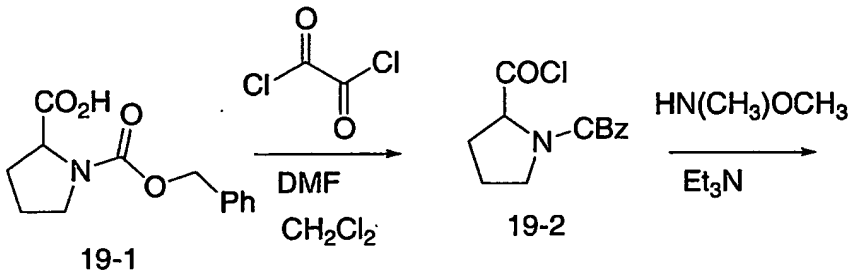
To an 8 mL vial was placed 1-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (15-3) (59 mg, 0.10 mmol), 3,4-diaminopyridine (11.1 mg, 0.10 mol) and dissolved in EtOH

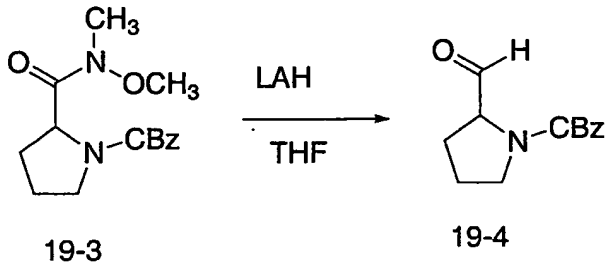
(3 mL). The vial was placed in a J-KEM heater/shaker block and warmed to 90 degrees for 9 hours. After this time, the vials were cooled and concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the TFA salts of (18-1) and (18-2) as brown solids.

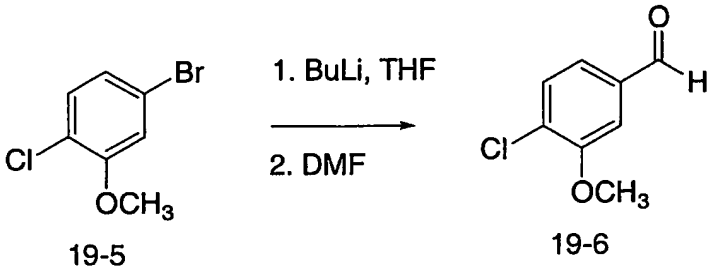
(18-1): Analytical LCMS: single peak (214 nm) at 2.220 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^1H NMR (400 MHz, CD_3OD): δ 9.64 (d, *J*=4 Hz, 1H), 8.85 (dd, *J*=6.2, 0.9 Hz, 1H), 8.22 (dd, *J*=6.1, 2.0 Hz, 1H), 7.58 (m, 4H), 7.46 (m, 1H), 7.38 (m, 2H), 7.28 (m, 1H), 7.07 (d, *J*=2.6 Hz, 3H), 4.59 (m, 1H), 4.43 (s, 2H), 3.60 (d, *J*=12.5 Hz, 2H), 3.28 (t, *J*=11.1 Hz, 2H), 2.82 (q, J=12.5 Hz, 2H), 2.08 (d, *J*=13.4 Hz, 2H). HRMS, calc'd for $C_{32}H_{29}N_6O$(M+H), 513.2393; found 512.2393.

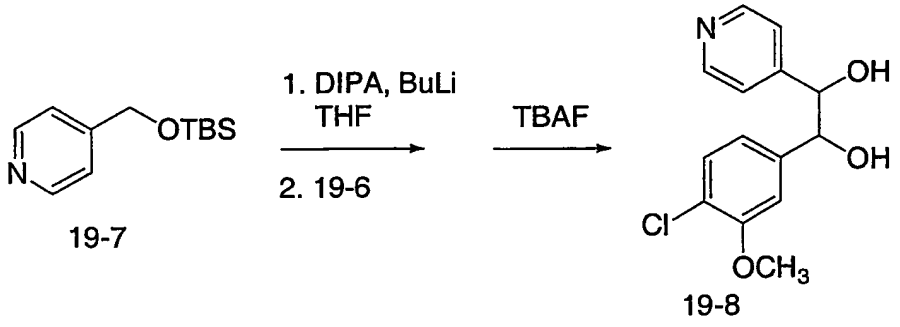
(18-2): Analytical LCMS: single peak (214 nm) at 2.410 min (CH_3CN/H_2O/1%TFA, 4 min gradient). ^1H NMR (400 MHz, CD_3OD): δ 9.60 (d, *J*=4 Hz, 1H), 8.81 (dd, *J*=6.2, 0.9 Hz, 1H), 8.20 (dd, *J*=6.1, 2.0 Hz, 1H), 7.58 (m, 4H), 7.46 (m, 1H), 7.38 (m, 2H), 7.28 (m, 1H), 7.07 (d, *J*=2.6 Hz, 3H), 4.59 (m, 1H), 4.43 (s, 2H), 3.60 (d, *J*=12.5 Hz, 2H), 3.28 (t, *J*=11.1 Hz, 2H), 2.82 (q, J=12.5 Hz, 2H), 2.08 (d, *J*=13.4 Hz, 2H). HRMS, calc'd for $C_{32}H_{29}N_6O$(M+H), 513.2393; found 512.2391.

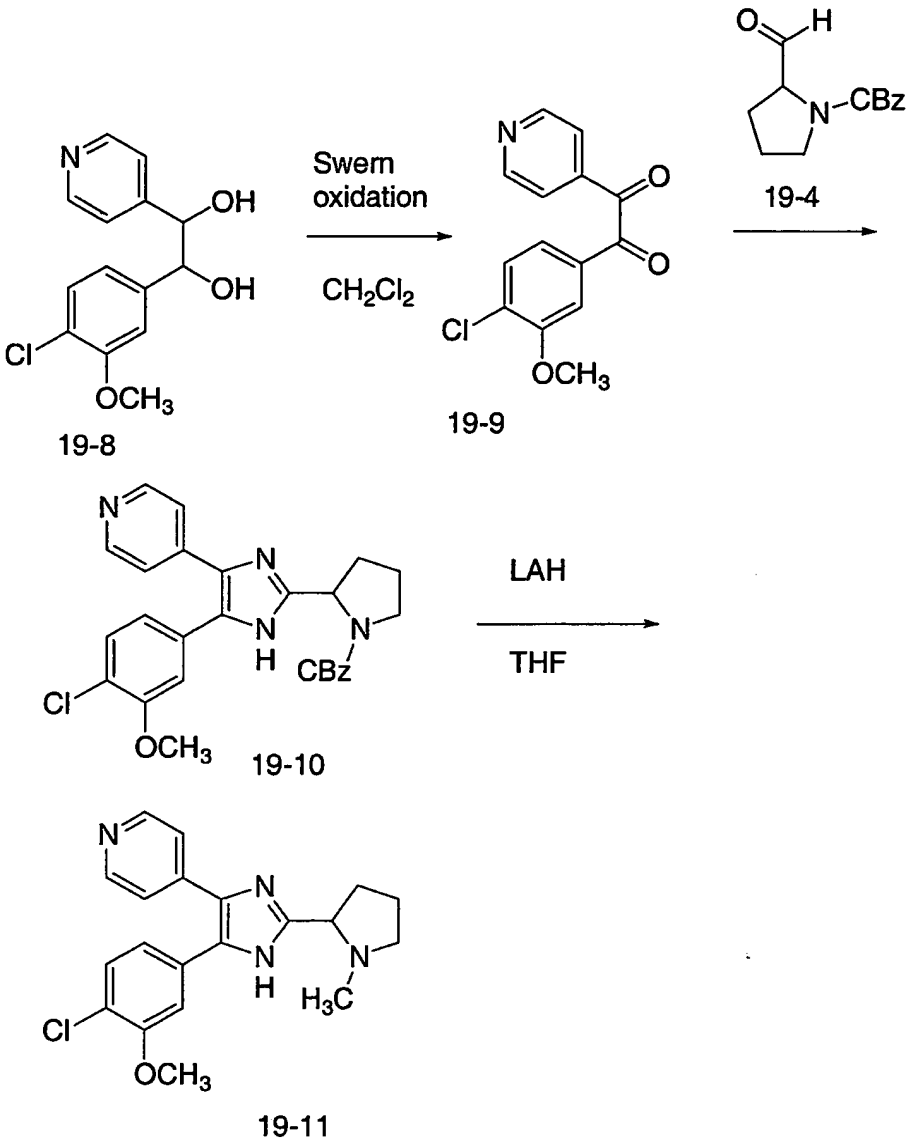
5 EXAMPLE 19


CO2H
O
N
O
Ph
19-1
O
Cl
Cl
O
DMF
CH2Cl2
COCl
N-CBz
19-2
HN(CH3)OCH3
Et3N


CH3
O
N
OCH3
N-CBz
19-3
LAH
THF
O
H
N-CBz
19-4


Br
Cl
OCH3
19-5
1. BuLi, THF
2. DMF
O
H
Cl
OCH3
19-6


OTBS
N
19-7
1. DIPA, BuLi
THF
2. 19-6
TBAF
N
OH
OH
Cl
OCH3
19-8



Step 1: N-benzyloxycarbonyl-2-pyrrolidine-N-methoxy-N-methylcarboxamide (19-3)

N-benzyloxycarbonylproline (25g, 0.116moles) and oxalyl chloride (10.12mL) was dissolved in 310 mL of CH_2Cl_2 and DMF (0.8 mL) and the mixture stirred at room temperature for 2 hours. At the end of this time the solvent was evaporated and the residue was dissolved in 400mL of CH_2Cl_2 and the solution cooled to 0°C. N,O-dimethylhydroxylamine hydrochloride (11.32 g, 0.116 moles) was

added, followed by dropwise addition of Et_3N (35.8 mL). The solution was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was further diluted with 300 mL of CH_2Cl_2 and poured into a bicarbonate solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and filtered. The organic solvents were evaporated and the residue suspended in a EtOAc/CH_2Cl_2/MeOH mixture. The mixture was filtered and the filtrate concentrated under vacuum and redissolved/filtered. The resulting organic soluble residue was purified on a silica gel column (70% EtOAc in hexane) to provide compound (19-3).

Step 2: N-benzyloxycarbonyl-2-pyrrolidine carboxaldehyde (19-4)

Compound (19-3) (25 g) was dissolved in 200 mL of THF and the solution cooled to 0°C. The solution was flushed with Ar and $LiAlH_4$ (49 mL of 1M solution) was added and the reaction mixture was stirred for 12 hours. An additional 0.25 eq. of the $LiAlH_4$ solution was added and the reaction mixture was stirred an additional 20 minutes. At the end of this time the reaction was quenched by the addition of 2 mL of water and diluted with EtOAc. The aluminum salts were removed by filtration and the filtrate was ashed with potassium sulfate solution, brine and then dried over Mg_2SO_4. The mixture was then filtered and concentrated under vacuum. The residue was purified on a silica gel column (20% EtOAc in hexane) to provide compound (19-4).

Step 3: 4-chloro-3-methoxybenzaldehyde (19-6)

5-Bromo-2-chloroanisole (19-5) (2.2 g) was dissolved in 200 mL of THF and the solution cooled to -78°C. Butyl lithium (4.4 mL of 2.5M solution) was added slowly, the reaction solution was stirred 5 minutes and DMF (0.93 mL) was added slowly. The reaction mixture was stirred briefly and then poured over sodium bicarbonate and ice. The aqueous mixture was extracted with EtOAc, the organic layer was washed with brine, dried over MgSO4 and filtered. The filtrate was concentrated under vacuum and the residue then purified by silica gel chromatography 1:9 EtOAc:hexane to provide the aldehyde (19-6) as a white solid..

Step 4: 1-(4-Chloro-3-methoxyphenyl)-2-pyridin-4-yl-ethane-1,2-diol (19-8)

To a stirring solution of diisopropylamine (14.4 mL, 110 mmol) in tetrahydrofuran (400 mL) at -78°C was added, dropwise, n-butyllithium (44 mL of a

2.5 M solution in tetrahydrofuran). After ten minutes, a solution of 4-pyridylcarbinol *t*-butyldimethylsilyl ether (22.3 g, 100 mmol) in tetrahydrofuran (80 mL) was added dropwise and the temperature allowed to rise to -15°C. The solution was again cooled to -78°C and a solution of 4-chloro-3-methoxybenzaldehyde (19-6) (17 g, 100 mmol) in tetrahydrofuran (60 mL) added dropwise. After the solution was allowed to warm to room temperature, it was poured into saturated aqueous sodium hydrogen carbonate (2 L). The aqueous layer was extracted with ethyl acetate (3x400 mL), the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting oil was dissolved in tetrahydrofuran and to this solution was added tetrabutylammonium fluoride (120 mL of a 1.0 M solution in tetrahydrofuran) dropwise. After ten minutes, the reaction mixture was concentrated at reduced pressure and the resulting oil chromatographed on silica gel, eluting with 95:5 to 90:10 dichloromethane:methanol to give the title compound as a mixture of diastereomeric diols (19-8) which was used without further purification.

Step 5: 1-(3,4-Dichlorophenyl)-2-pyridin-4-yl-ethane-1,2-dione (19-9)

To a stirring solution of methyl sulfoxide (28.7 mL, 403 mmol) in dichloromethane (600 mL) at -78°C was added trifluoroacetic anhydride (42.7 mL, 302 mmol) dropwise. After ten minutes, 1-(4-Chloro-3-methoxyphenyl)-2-pyridin-4-yl-ethane-1,2-diol (19-8) (25.6 g, 91.5 mmol) in dichloromethane (200 mL) was added dropwise. After another ten minutes, triethylamine (79 mL, 567 mmol) was added dropwise and the reaction mixture immediately warmed to -10°C and poured into water. The aqueous layer was extracted with methylene chloride and the organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The resulting solid was triturated with ether to give the dione (19-9) as a yellow solid.

Step 6: 2-[5-(4-chloro-3-methoxyphenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-pyrrolidine-1-benzyloxycarbonyl ester (19-10)

Compound (19-4) (2.0 g) and the dione (19-9) (2.76 g) were dissolved in 20 mL of acetic acid and the mixture was heated to 100°C. Ammonium acetate (15.48 g) was added slowly and the reaction mixture stirred for 2 hours. The mixture was then poured into ice and the ice slurry was extracted with 2:1 EtOAc:aqueous NH_4OH. The aqueous layer was extracted 4 times with EtOAc and the combined organic layers were washed with brine and dried over Mg_2SO_4. The mixture was

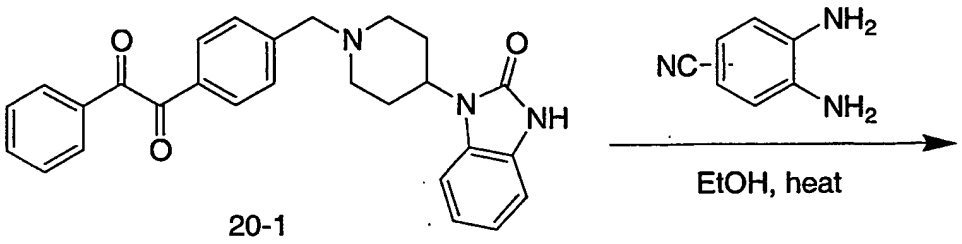
filtered and concentrated under vacuum to provide a brown foam. The residue was purified on a silica gel column (3% MeOH in CH_2Cl_2) and the main fractions were repurified under the same silica gel conditions to provide compound (19-10).

Step 7: 1-methyl-2-[5-(4-chloro-3-methoxyphenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-pyrrolidine (19-11)

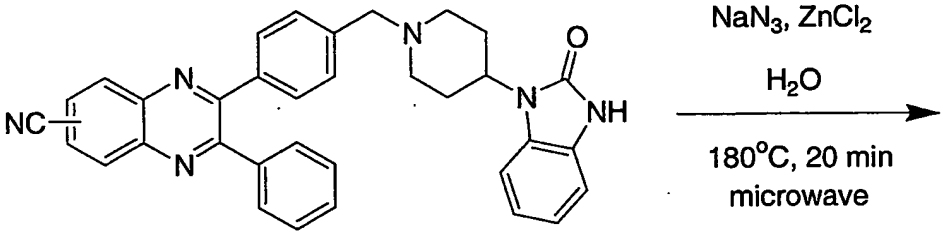
Compound (19-10) (580 mg, 1.19 mmol) was dissolved in 10 mL THF and the solution flushed with Ar. A 1.0 M $LiAlH_4$ solution (1.79 mL, 1.79 mmol) was added and the reaction mixture was heated to 70°C. After stirring the reaction at 70°C for 2.5 hours an additional 1 equiv. (1.19 mL) of the $LiAlH_4$ solution was added. The reaction was then quenched with of water and the mixture diluted with EtOAc. The mixture was then poured into a saturated sodium bicarbonate solution and the separated aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Mg_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (6% to 10% MeOH in CH_2Cl_2 gradient) to provide the titled compound (19-11).

5

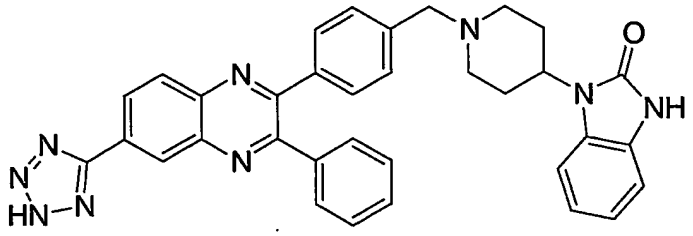
EXAMPLE 20



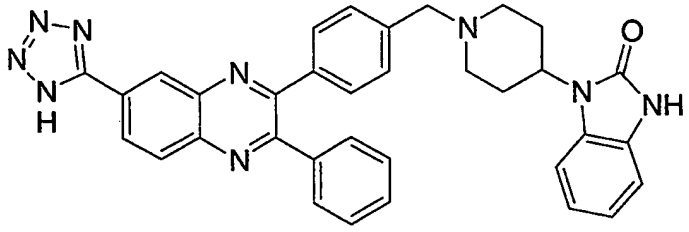
20-1



20-2



20-3



20-4

3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carbonitrile (20-2) and 3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-7-carbonitrile (20-2)

1-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (20-1) (176 mg, 0.4 mmol), and 3,4-diaminobenzonitrile (81 mg, 0.6 mmol) were dissolved in 2 mL of MeOH/HOAc (9/1) in an 8 mL vial. The mixture solution is stirred at rt for 3 hours. After this time, the reaction was concentrated in vaccuo. The crude material was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford 149.1 mg of the TFA salt of the un-separatable mixture of 6- and 7- carbonitriles (20-2) as a brown solid. Analytical LCMS: single peak (214 nm) at 2.634 min (CH_3CN/H_2O/1%TFA, 4 min gradient), M+1 peak *m/e* 537.3.

1-(1-{4-[3-phenyl-6-(1*H*-tetrazol-5-yl)quinoxalin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (20-3)

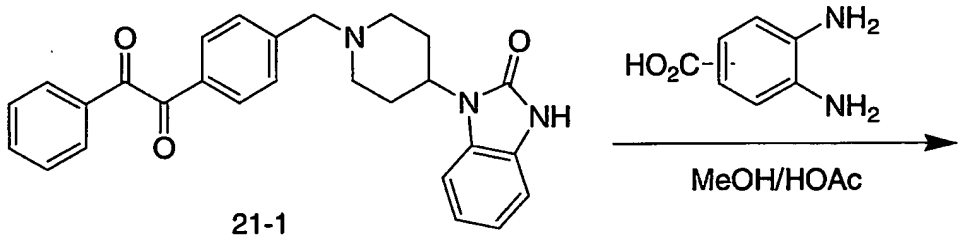
A mixture of 3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carbonitrile (20-2) and 3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-7-carbonitrile (20-2) (53.6 mg, 0.08 mmol), 2 M NaN_3 (0.5 mL, 1.0 mmol), and 2 M $ZnBr_2$ (0.5 mL, 1.0 mmol) was charged in a microwave tube and microwaved at 180 °C for 20 min. After this time, the reaction was cooled to rt and the precipitate is collected by centrifuge. The crude material (precipitate) was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford 27 mg of the TFA salt of the pure 1-(1-{4-[3-phenyl-6-(1*H*-tetraazol-5-yl)quinoxalin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (20-3) as a yellow-brown solid. Analytical LCMS: single peak (214 nm) at 2.320 min (CH_3CN/H_2O/1%TFA, 4 min gradient), M+1 peak *m/e* 580.3. ^{1}H NMR (500 MHz, DMSO-d6): δ 10.93 (s, 1H), δ 9.71 (s, 1H), 8.84 (d, *J*=2.0 Hz, 1H), 8.53 (dd, *J*=8.5, 1.9 Hz, 1H), 8.37 (d, *J*=8.5 Hz, 1H), 7.65(d, *J*=8.8 Hz, 2H), 7.54-7.58(m, 4H), 7.42-7.46 (m, 3H), 7.28(d, *J*=7.9 Hz, 1H), 7.01-7.04 (m, 3H), 4.48-4.52 (m, 1H), 4.40 (s, 2H), 3.52 (d, *J*=12.8 Hz, 2H), 3.22 (t, *J*=13.8 Hz, 2H), 2.67 (q, *J*=13.9 Hz, 2H), 1.96 (d, *J*=13.8 Hz, 2H).

1-(1-{4-[3-phenyl-7-(1*H*-tetrazol-5-yl)quinoxalin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (20-4)

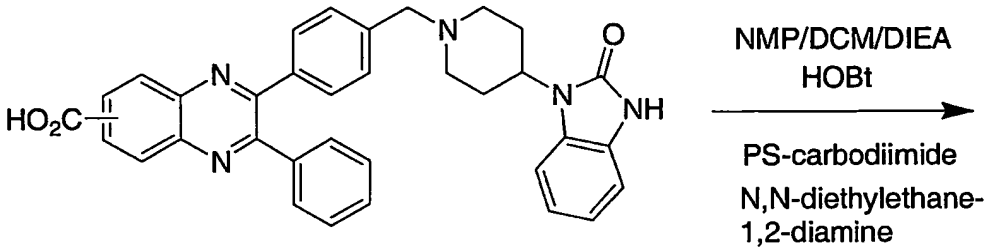
A mixture of 3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carbonitrile (20-2) and 3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-7-carbonitrile (20-2) (53.6 mg, 0.08 mmol), 2 M NaN_3 (0.5 mL, 1.0 mmol), and 2 M $ZnBr_2$ (0.5 mL, 1.0 mmol) was charged in a microwave tube and microwaved at 180 °C for 20 min. After this time, the reaction was cooled to rt and the precipitate is collected by centrifuge. The crude material (precipitate) was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford 30 mg of the TFA salt of the pure 1-(1-{4-[3-phenyl-7-(1*H*-tetraazol-5-yl)quinoxalin-2-yl]benzyl}piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (20-4) as a yellow-brown solid. Analytical LCMS: single peak (214 nm) at 2.381 min (CH_3CN/H_2O/1%TFA, 4 min gradient), M+1 peak *m/e* 580.3. ^{1}H NMR (500 MHz, DMSO-d6): δ 10.92 (s, 1H), δ 9.81 (s, 1H), 8.82 (d, *J*=1.9 Hz, 1H), 8.53 (dd, *J*=8.7, 1.9 Hz, 1H), 8.40 (d, *J*=8.7 Hz, 1H), 7.66(d, *J*=7.9 Hz, 2H), 7.58(d, *J*=8.4 Hz, 2H), 7.53(d, *J*=7.9 Hz, 2H), 7.45 (t, *J*=7.4 Hz, 1H), 7.40 (t, *J*=7.8 Hz, 2H), 7.29(d, *J*=6.7 Hz, 1H), 7.00-7.03 (m, 3H), 4.49-4.52 (m, 1H), 4.40 (s, 2H), 3.52 (d, *J*=11.5 Hz, 2H), 3.22 (t, *J*=13.2 Hz, 2H), 2.68 (q, *J*=13.1 Hz, 2H), 1.96 (d, *J*=13.3 Hz, 2H).

5

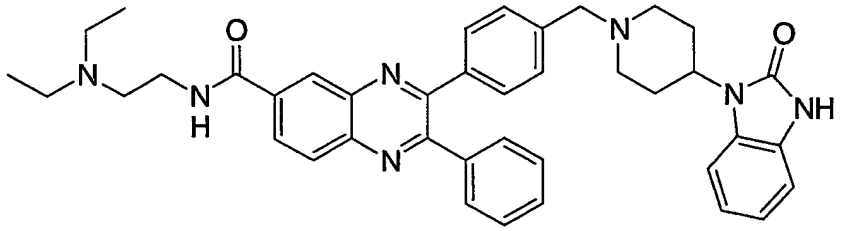
EXAMPLE 21



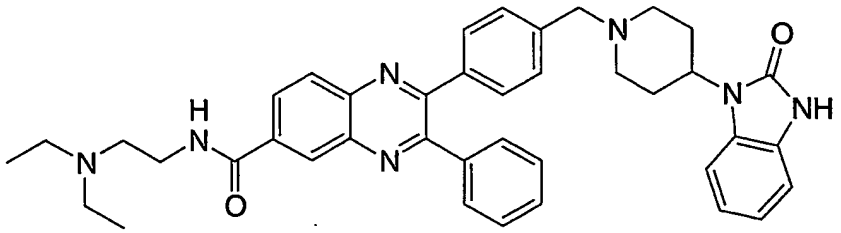
21-1



21-2



21-3



21-4

3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carboxylic acid (21-2) and 2-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-3-phenylquinoxaline-6-carboxylic acid (21-2)

To 1-(4-{[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)pipepridin-1-yl]methyl}phenyl)-2-phenylethane-1,2-dione (21-1) (4.39 g, 10 mmol, in 40 mL of MeOH/HOAc (9/1)) was added 4-diaminobenzoic acid (1.55 g, 10.2 mmol, in 20 mL of DMSO/MeOH (3/1)) dropwise with stirring. After addition of 4-diaminobenzoic acid, the reaction was stirred for 2h at room temperature. The solution precipitated and LCMS indicated that the reaction was completed. The reaction mixture was poured into water (150 mL). The precipitate was collected by centrifuge and washed with water (3x). LCMS indicated that the precipitate was the desired product of the two regioisomers (7-1). Analytical LCMS: double peaks (214 nm) at 2.317 and 2.388 min (CH_3CN/H_2O/1%TFA, 4 min gradient), M+1 peak at 2.353 min (*m/e* 556.3) and 2.428 min (*m/e* 556.3). The product was frozen dry (5.2 g) and used in the next step without further purification.

N-[2-(diethylamino)ethyl]-3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carboxamide (21-3) and *N*-[2-(diethylamino)ethyl]-2-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-3-phenylquinoxaline-6-carboxamide (21-4)

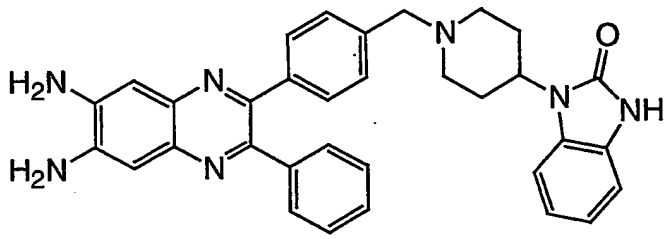
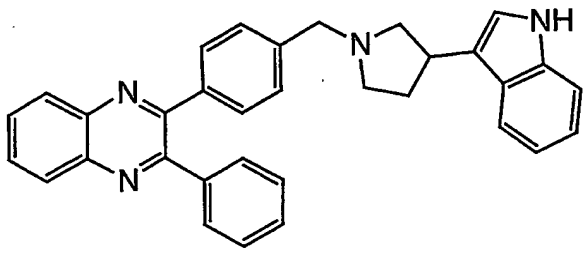
The mixture of 3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carboxylic acid (21-2) and 2-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-3-phenylquinoxaline-6-carboxylic acid (21-2), 222 mg (0.4 mmol) was dissolved in NMP/DCM/DIEA (10 mL, 9/1). To this solution was added HOBt (152 mg, 1.0 mmol), PS-carbodiimide (1.1 g, 1.3 mmol), and DCM (5 mL). The resultant mixture was shaken 0.5h. After this time, *N*,*N*-diethylethane-1,2-diamine (232 mg, 2.0 mmol) was added to the NMP solution and the reaction was shaken over weekend. After this time, LCMS indicated that the coupling reaction was complete. The resin was filtered and washed with MeOH (3X15 mL). The combined solution was dried to give a brown residue. This residue was then purified on an Agilent 1100 series Mass Guided HPLC purification system to afford the two pure regioisomers *N*-[2-(diethylamino)ethyl]-3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carboxamide (21-3) (50.7 mg) and *N*-[2-

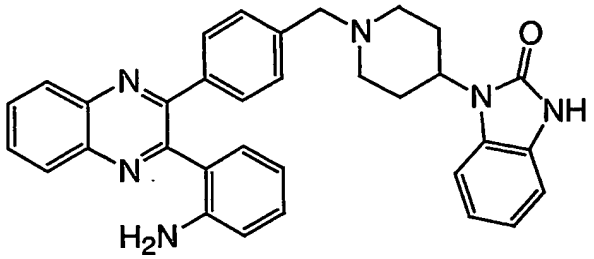
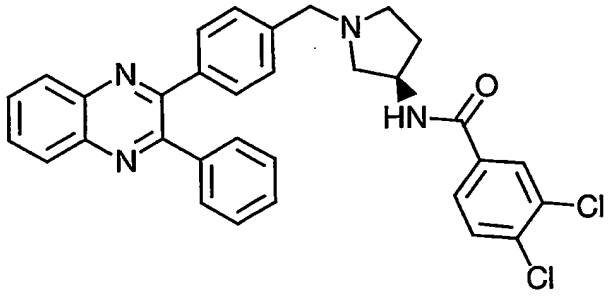
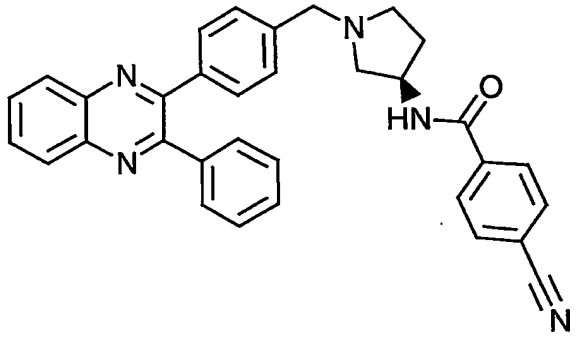
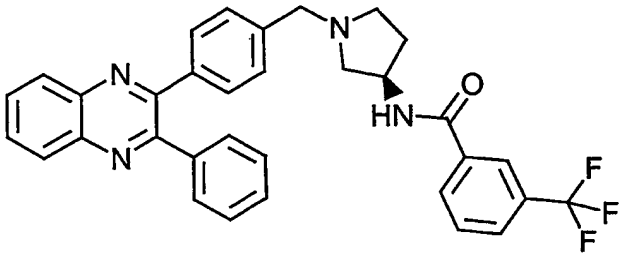
(diethylamino)ethyl]-2-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-3-phenylquinoxaline-6-carboxamide (21-4) (119 mg). Analytical data for *N*-[2-(diethylamino)ethyl]-3-(4-{[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]methyl}phenyl)-2-phenylquinoxaline-6-carboxamide (21-3): Analytical LCMS: single peak (214 nm) at 2.084 min ($CH_3CN/H_2O/1\%TFA$, 4 min gradient). ^1H NMR (500 MHz, DMSO-d6): δ 10.96 (s, 1H), 10.10 (s, 1H), 9.50 (s, 1H), 9.20 (t, *J*=5.9 Hz, 1H), 8.69 (s, 1H), 8.26-8.34 (m, 2H), 7.49-7.66 (m, 6H), 7.35-7.47 (m, 3H), 7.26-7.32 (m, 1H), 6.97-7.04 (m, 3H), 4.48-4.58 (m, 1H), 4.40 (s, 2H), 3.72 (q, *J*=6.1 Hz, 2H), 3.50 (d, *J*=11.7 Hz, 2H), 3.34(q, *J*=5.4 Hz, 2H), 3.20-3.30 (m, 6H), 2.67 (q, *J*=14.5 Hz, 2H), 1.96 (d, *J*=13.0 Hz, 2H), 1.25 (t, *J*=7.5 Hz, 6H).. HRMS, calc'd for $C_{40}H_{44}N_7O_2$ (M+H), 654.3551; found 654.3573.

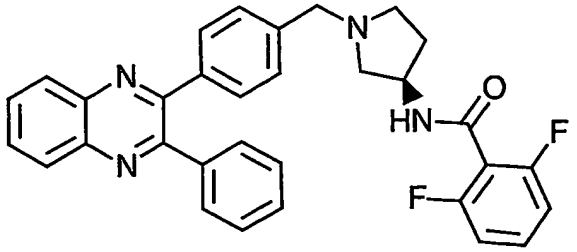
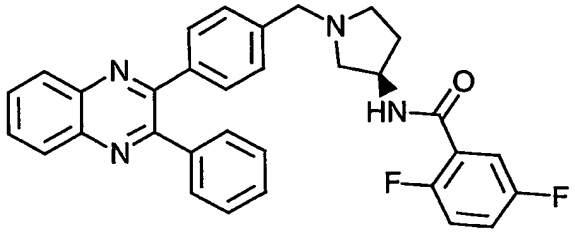
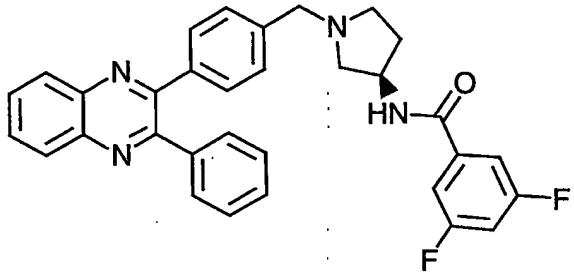
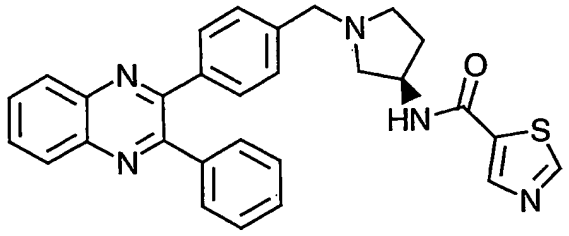
EXAMPLE 22

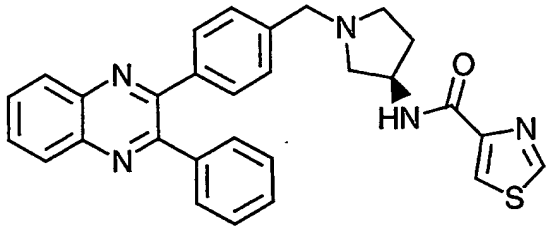
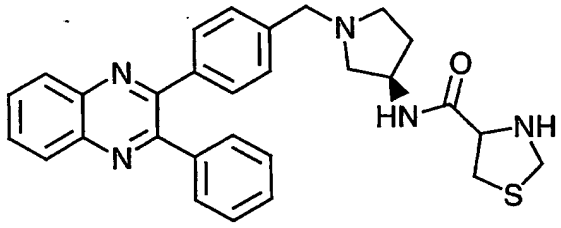
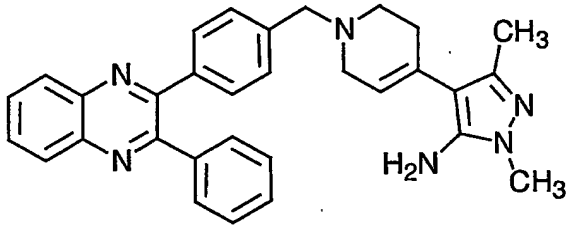
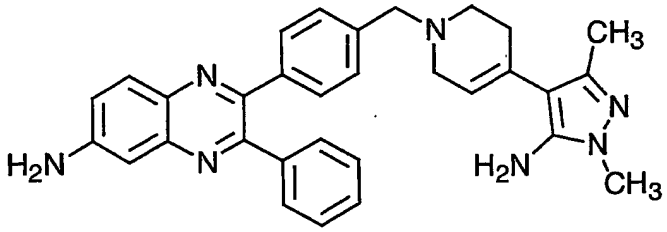
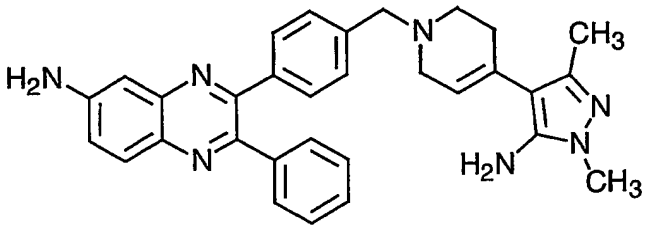
Other compounds shown in Table 3 were synthesized as shown in Schemes 7-8 above. Unless otherwise stated, the TFA salt of the compound shown was isolated by Mass Guided HPLC purification.

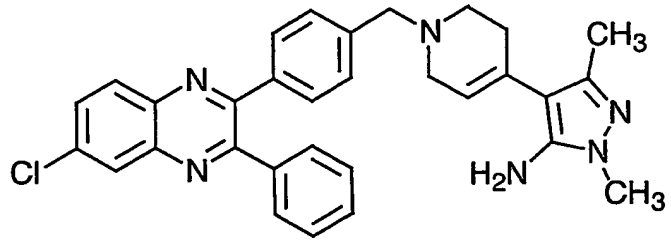
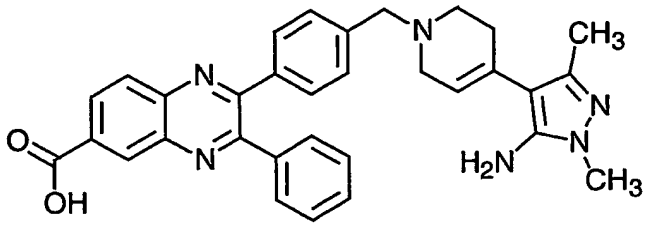
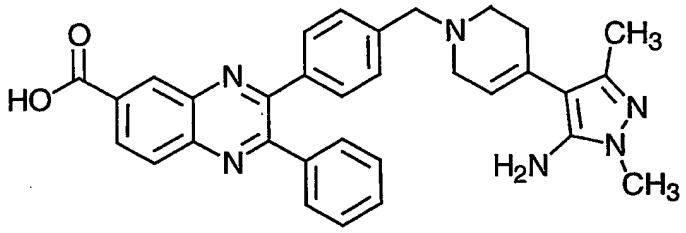
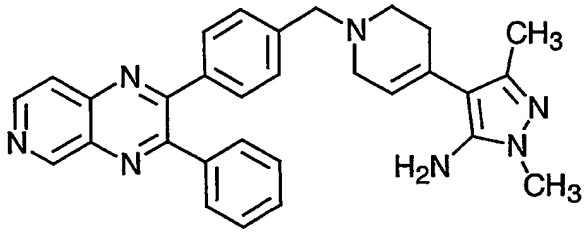
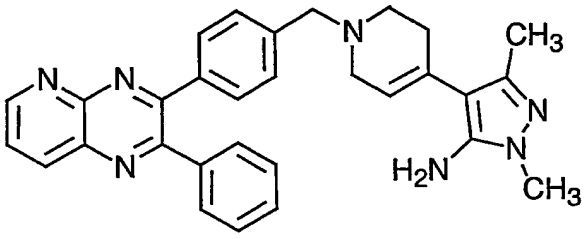
Table 3

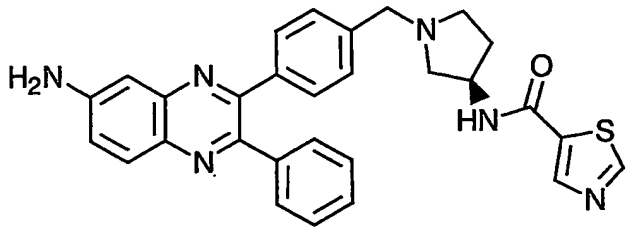
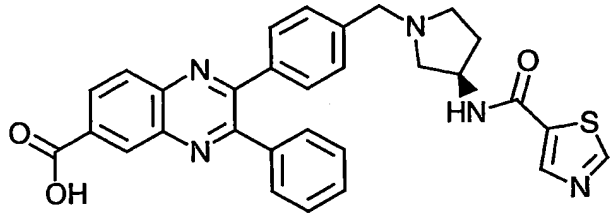
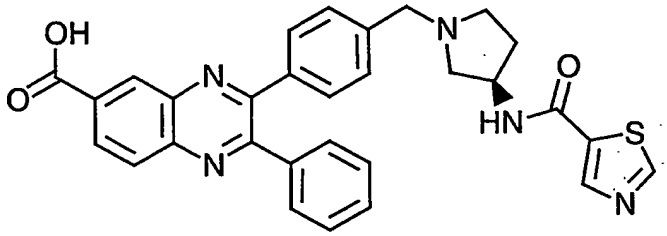
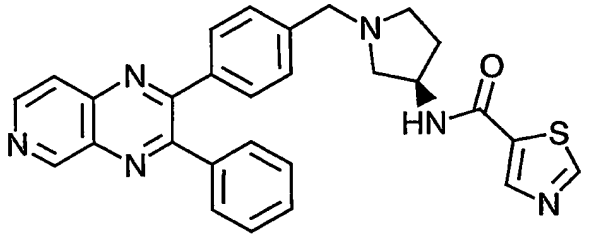
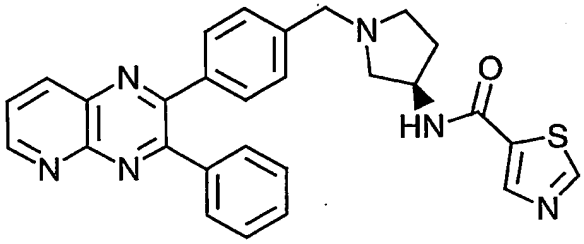
Compound	MS M+1
	541.2590
	480.2314

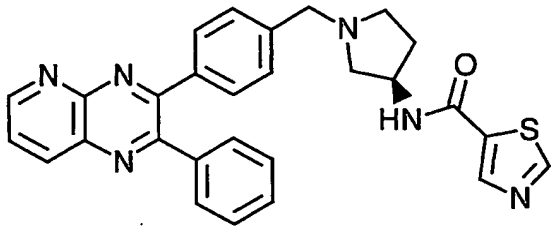
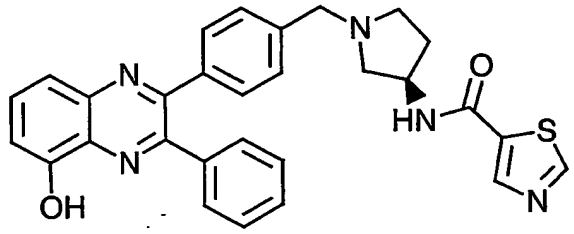
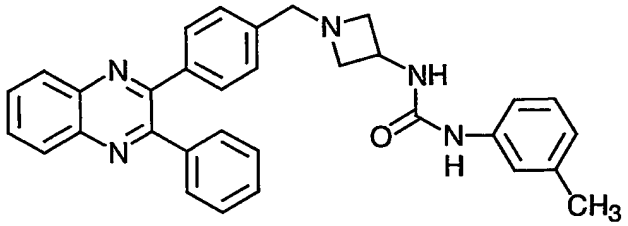
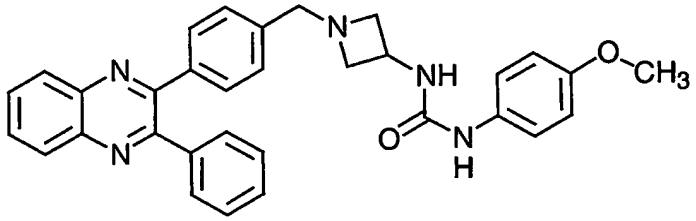
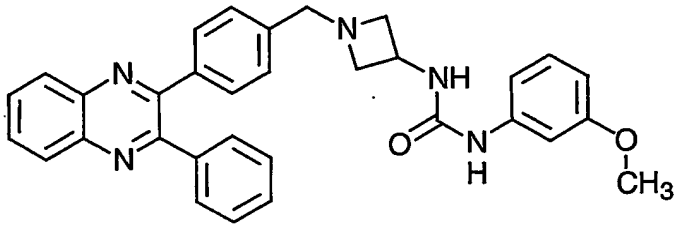
	526.2481
	552.1483
	509.2215
	552.2185

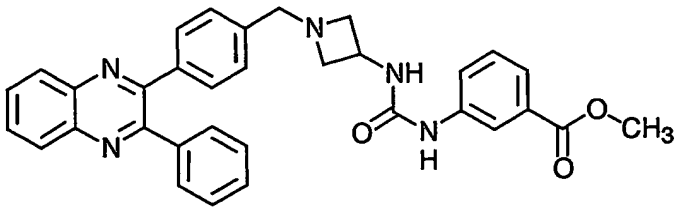
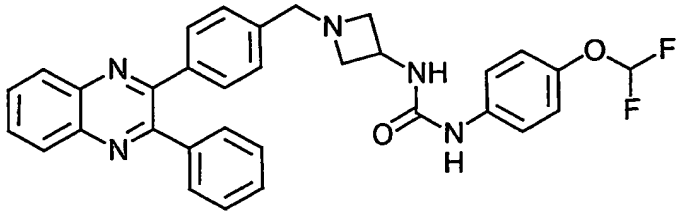
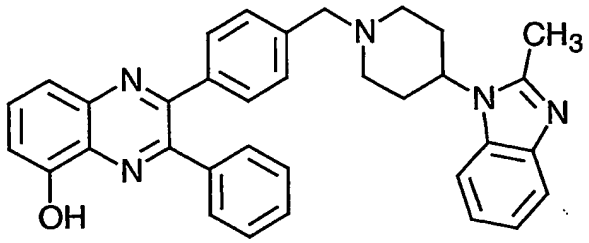
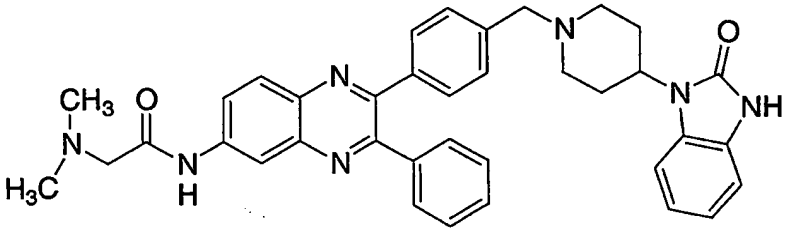
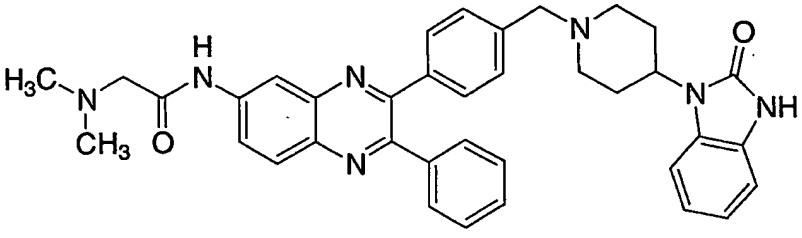
	520.2106
	520.2106
	520.2106
	491.1779

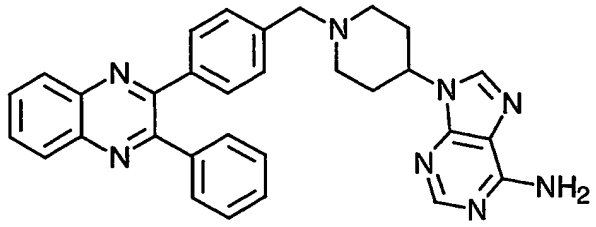
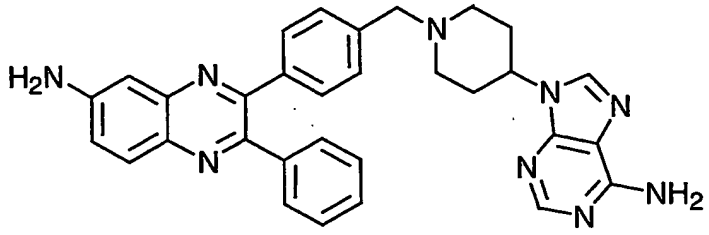
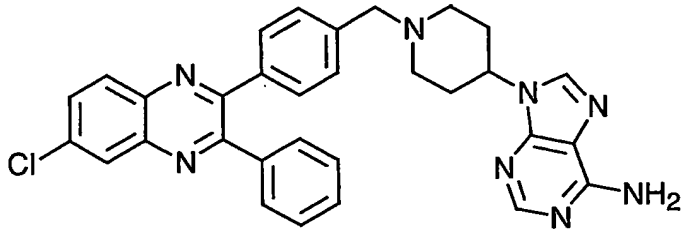
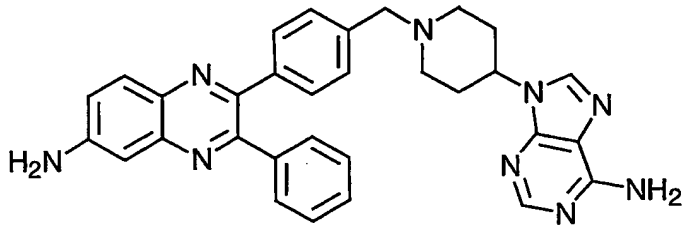
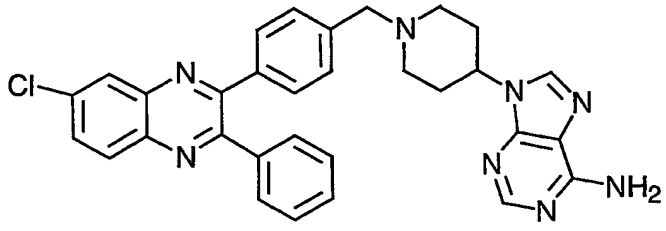
	491.1779
	495.2092
	486.2532
	501.2641
	501.2641

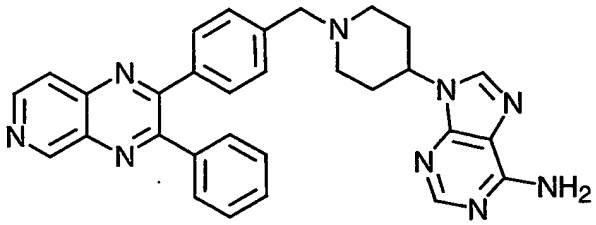
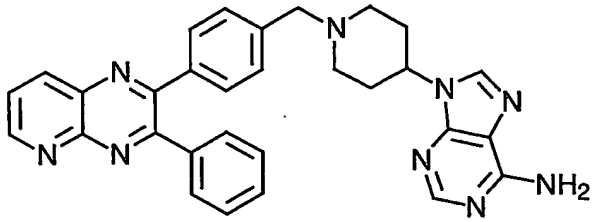
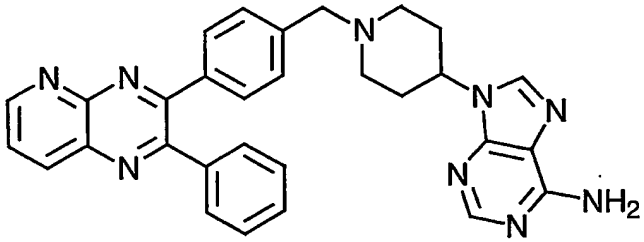
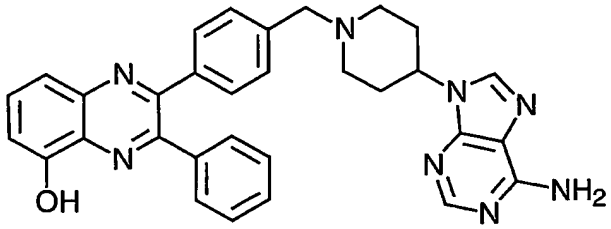
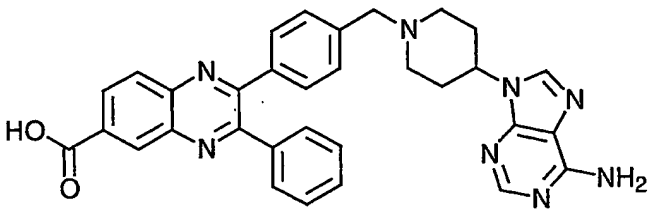
	521.3
	530.2430
	530.2430
	487.2484
	487.2484

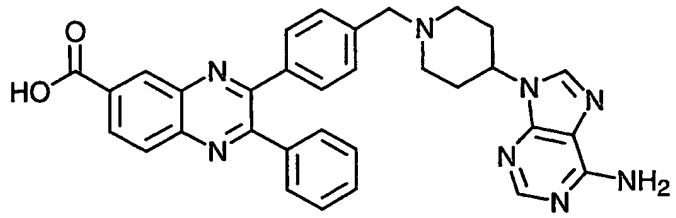
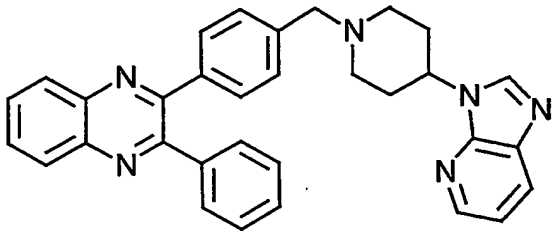
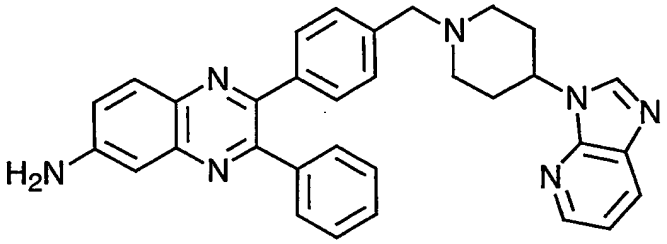
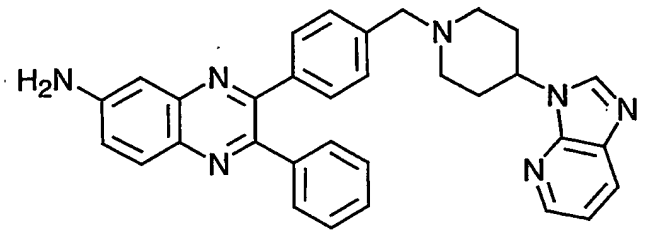
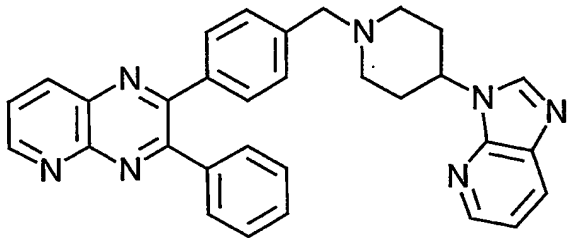
	506.1888
	535.1678
	535.1678
	492.1732
	492.1732

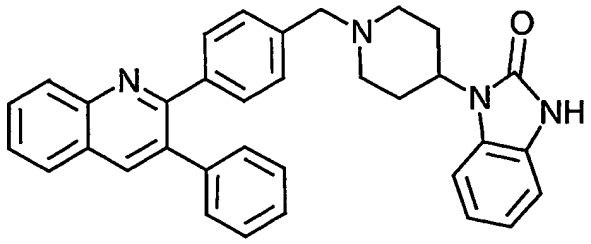
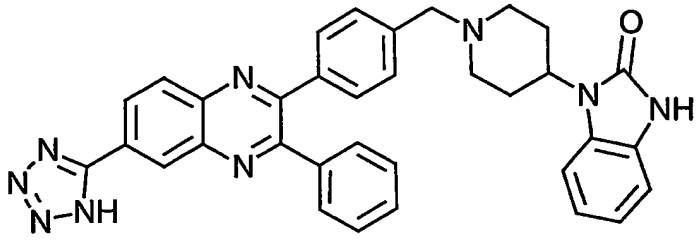
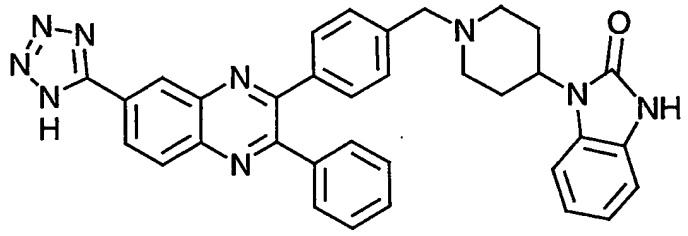
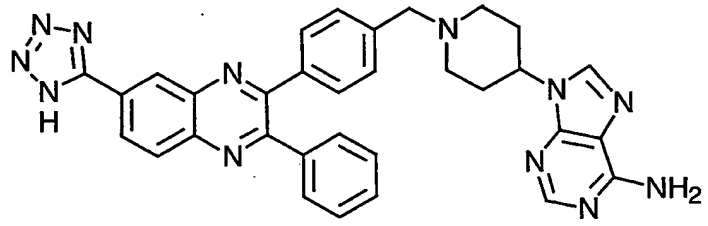
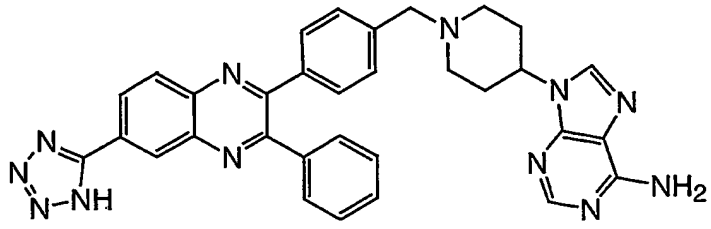
	492.1732
	507.1729
	499.2372
	515.2321
	515.2321

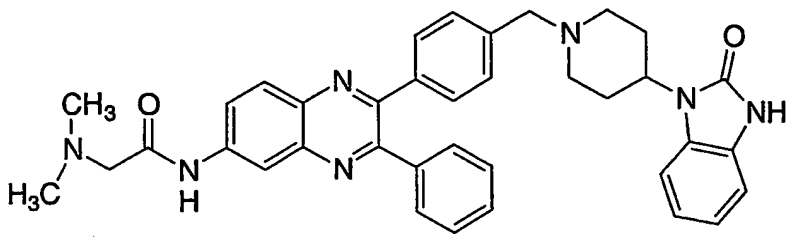
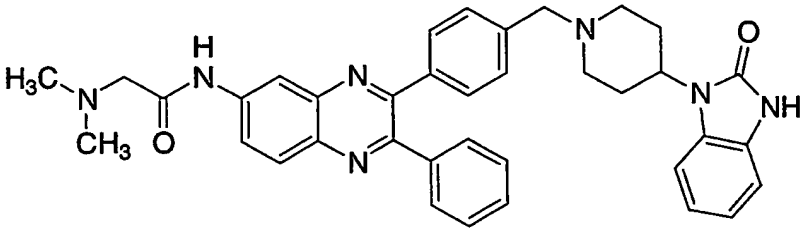
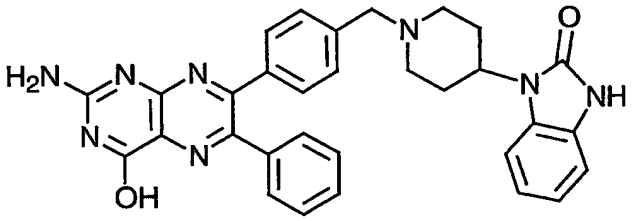
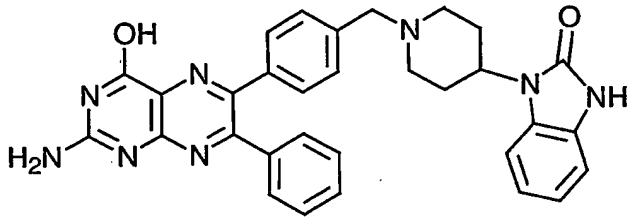
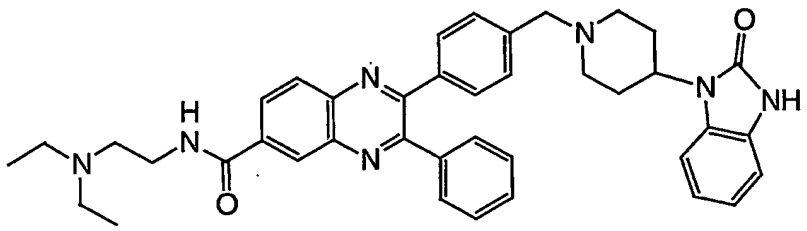
	543.2270
	551.2164
	525.2528
 	611.3008

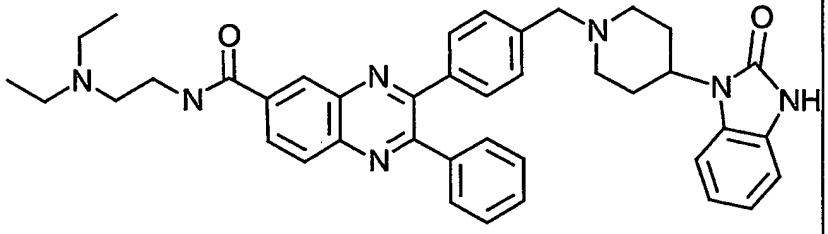
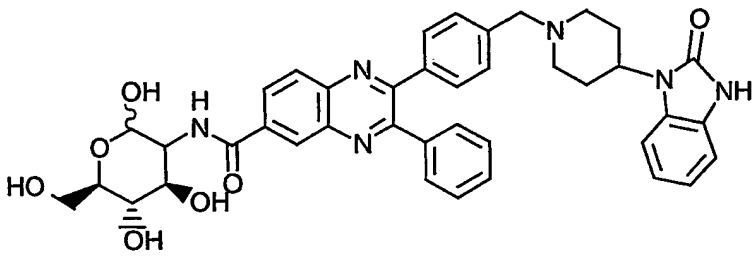
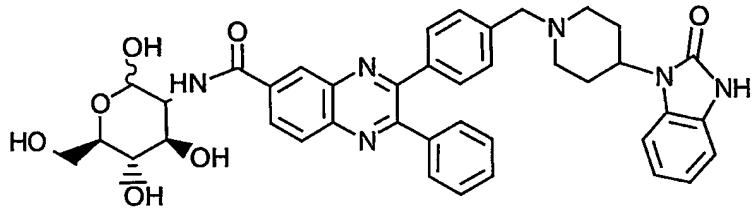
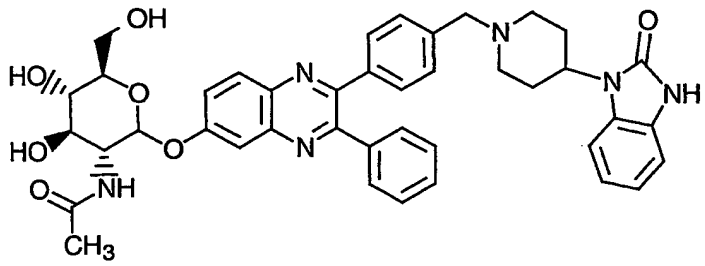
	512.2436
	527.2545
	547.2
	527.2545
	547.2

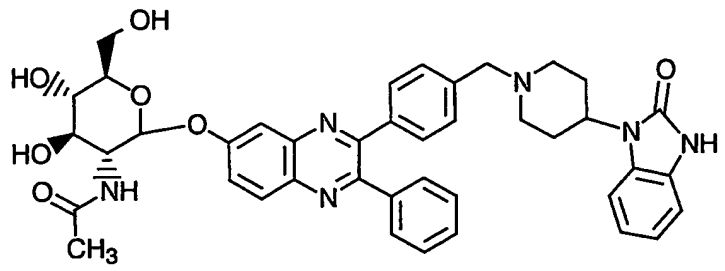
	513.2389
	513.2389
	513.2389
	528.2386
	556.2335

	556.2335
	496.2375
	511.2484
	511.2484
	497.2328

	510.2419
	579.2495
	579.2495
	580.2559
	581.3

	611.3008
	611.3008
 	544.2335
	653.3478

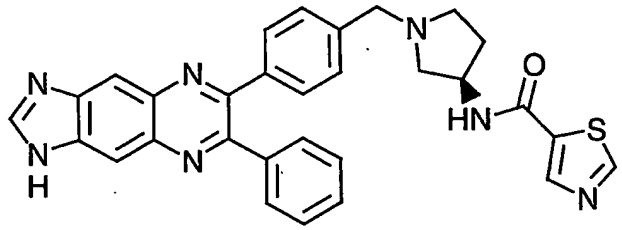
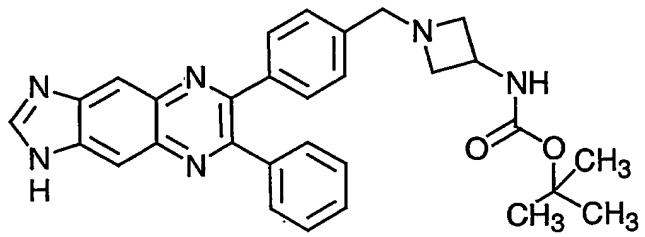
	653.3478
	716.2958
	716.2958
	730.3115

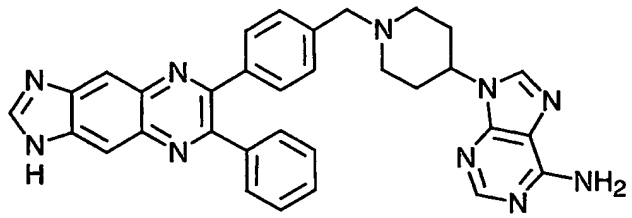
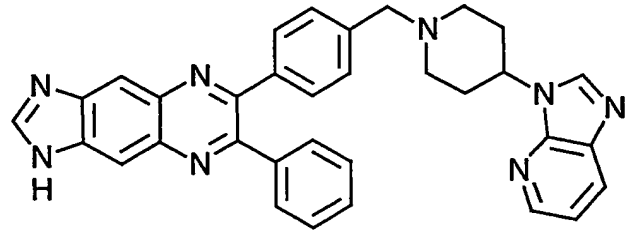
	730.3115

EXAMPLE 23

Compounds in Table 4 were synthesized as shown in Schemes 9-10 above. Unless otherwise stated, the TFA salt of the compound shown was isolated by Mass Guided HPLC purification.

Table 4

Compound	MS M+1
	531.1841
	506.2430

	552.2498
	536.2436

EXAMPLE 24

Cloning of human Akt1, Akt2, Akt3, ΔPH-Akt1, ΔPH-Akt2, ΔPH-Akt3 and minimal ΔPH Akt1

The pS2neo vector (deposited in the ATCC on April 3, 2001 as PTA-3253) was prepared as follows: The pRmHA3 vector (prepared as described in *Nucl. Acid Res.* 16:1043-1061 (1988)) was cut with BglII and a 2734 bp fragment was isolated. The pUChsneo vector (prepared as described in *EMBO J.* 4:167-171 (1985)) was also cut with BglII and a 4029 bp band was isolated. These two isolated fragments were ligated together to generate a vector termed pS2neo-1. This plasmid contains a polylinker between a metallothionein promoter and an alcohol dehydrogenase poly A addition site. It also has a neomycin resistance gene driven by a heat shock promoter. The pS2neo-1 vector was cut with Psp5II and BsiWI. Two complementary oligonucleotides were synthesized and then annealed (CTGCGGCCGC (SEQ.ID.NO.: 1) and GTACGCGGCCGCAG (SEQ.ID.NO.: 2)). The cut pS2neo-1 and the annealed oligonucleotides were ligated together to generate a second vector, pS2neo. Added in this conversion was a NotI site to aid in the linearization prior to transfection into S2 cells.

Human Akt1 gene was amplified by PCR (Clontech) out of a human spleen cDNA (Clontech) using the 5' primer: 5'CGCGAATTCAGATCTACCATGAGCGACGTGGCTATTGTG 3' (SEQ.ID.NO.: 3), and the 3' primer: 5'CGCTCTAGAGGATCCTCAGGCCGTGCTGCTGGC3' (SEQ.ID.NO.: 4). The 5' primer included an EcoRI and BglII site. The 3' primer included an XbaI and BamHI site for cloning purposes. The resultant PCR product was subcloned into pGEM3Z (Promega) as an EcoRI / Xba I fragment. For expression/purification purposes, a middle T tag was added to the 5' end of the full length Akt1 gene using the PCR primer: 5'GTACGATGCTGAACGATATCTTCG 3' (SEQ.ID.NO.: 5). The resulting PCR product encompassed a 5' KpnI site and a 3' BamHI site which were used to subclone the fragment in frame with a biotin tag containing insect cell expression vector, pS2neo.

For the expression of a pleckstrin homology domain (PH) deleted (Δ aa 4-129, which includes deletion of a portion of the Akt1 hinge region) version of Akt1 (termed ΔPH-Akt1), PCR deletion mutagenesis was done using the full length Akt1 gene in the pS2neo vector as template. The PCR was carried out in 2 steps using overlapping internal primers (5'GAATACATGCCGATGGAAAGCGACGGGGCTGAAGAGATGGAGGTG 3' (SEQ.ID.NO.: 6), and 5'CCCCTCCATCTCTTCAGCCCCGTCGCTTTCCATCGGCATG TATTC 3' (SEQ.ID.NO.: 7)) which encompassed the deletion and 5' and 3' flanking primers which encompassed the KpnI site and middle T tag on the 5' end. The final PCR product was digested with KpnI and SmaI and ligated into the pS2neo full length Akt1 KpnI / Sma I cut vector, effectively replacing the 5' end of the clone with the deleted version.

For expression of a minimal ΔPH (Δaa 1-110) version of Akt1, PCR was performed using full length Akt1 as template and the following PCR oligo primers; 5' PCR oligo = 5'CGCGGCGCGCCAGGTACCATGGAATACATGCCGATGGAAAAGAAGCAG GAGGAGGAGGAG 3' (SEQ.ID.NO.: 8) which encompassed a KpnI cloning site, the middle T antigen tag and the PH domain deletion. The 3' PCR oligo = 5'CGGAGAACACACGCTCCCGGG 3' (SEQ.ID.NO.: 9). The resultant PCR product was digested with KpnI and SmaI and ligated into the pPS2neo full length Akt1 KpnI / SmaI cut vector, effectively replacing the 5' end of the clone with the deleted version.

Human Akt3 gene was amplified by PCR of adult brain cDNA (Clontech) using the amino terminal oligo primer:
5' GAATTCAGATCTACCATGAGCGATGTTACCATTGTG 3' (SEQ.ID.NO.: 10);
and the carboxy terminal oligo primer :
5' TCTAGATCTTATTCTCGTCCACTTGCAGAG 3'(SEQ.ID.NO.: 11).
These primers included a 5' EcoRI / BglII site and a 3' XbaI / BglII site for cloning purposes. The resultant PCR product was cloned into the EcoRI and XbaI sites of pGEM4Z (Promega). For expression / purification purposes, a middle T tag was added to the 5' end of the full length Akt3 clone using the PCR primer: 5' GGTACCATGGAATACATGCCGATGGAAAGCGATGTTACCATTGTGAAG 3'(SEQ.ID.NO.: 12). The resultant PCR product encompassed a 5' KpnI site which allowed in frame cloning with the biotin tag containing insect cell expression vector, pS2neo.

For expression of a PH domain deleted (Δaa 4-128, which includes deletion of a portion of the Akt3 hinge region) version of Akt3 (termed ΔPH-Akt3), PCR was performed using the full length Akt3 as template and the following oligo primers; 5'PCR oligo =
5'CGCAGGTACCATGGAATACATGCCGATGGAAAGCGATGGAGAGGAAGA GATGGATGCC 3' (SEQ.ID.NO.: 13) which encompassed a KpnI cloning site, the middle T antigen tag and the deleted PH domain. The 3' PCR oligo =
5'CGCTCTAGATCTTATTCTCGTCCACTTGCAGAG 3' (SEQ.ID.NO.: 14).
The resultant PCR product was digested with KpnI and BamHI and ligated into the pS2neo full length Akt3 KpnI / BamHI cut vector, effectively replacing the 5' end of the clone with the deleted version.

Human Akt2 gene was amplified by PCR from human thymus cDNA (Clontech) using the amino terminal oligo primer:
5' AAGCTTAGATCTACCATGAATGAGGTGTCTGTC 3' (SEQ.ID.NO.: 15); and the carboxy terminal oligo primer:
5'GAATTCGGATCCTCACTCGCGGATGCTGGC 3' (SEQ.ID.NO.: 16). These primers included a 5' HindIII / BglII site and a 3' EcoRI / BamHI site for cloning purposes. The resultant PCR product was subcloned into the HindIII / EcoRI sites of pGem3Z (Promega). For expression / purification purposes, a middle T tag was added to the 5' end of the full length Akt2 using the PCR primer:
5'GGTACCATGGAATACATGCCGATGGAAAATGAGGTGTCTGTCATCAAAG

3' (SEQ.ID.NO.: 17). The resultant PCR product was subcloned into the pS2neo vector as described above.

For expression of a PH domain deleted (Δ aa 4-131, which includes deletion of a portion of the Akt2 hinge region) version of Akt2 (termed ΔPH-Akt2), PCR was performed using the full length Akt2 gene as template and the following oligo primers; 5' PCR oligo = 5'CGCAGGTACCATGGAATACATGCCGATGGAAAATGAGACGACTGAGGA GATGGAAGTGGC 3' (SEQ.ID.NO.: 18), which encompassed a KpnI cloning site, the middle T antigen tag and the deletion. The 3' PCR oligo = 5'CGCGAATTCGGATCCTCACTCGCGGATGCTGGC 3' (SEQ.ID.NO.: 19). The resultant PCR product was digested with KpnI and SmaI and ligated into the pS2neo full length Akt2 KpnI / SmaI cut vector, effectively replacing the 5' end of the clone with the deleted version.

EXAMPLE 25

Expression of human Akt1, Akt2, Akt3, ΔPH-Akt1, ΔPH-Akt2, ΔPH-Akt3 and minimal ΔPH Akt1

The DNA containing the cloned Akt1, Akt2, Akt3, ΔPH-Akt1, ΔPH-Akt2, ΔPH-Akt3 and ΔPH domain specific-Akt1 genes in the pS2neo expression vector was purified and used to transfect *Drosophila* S2 cells (ATCC) by the calcium phosphate method. Pools of antibiotic (G418, 500 μg/ml) resistant cells were selected. Cell were expanded to a 1.0L volume (~7.0 x 10^6 / ml), biotin and $CuSO_4$ were added to a final concentration of 50 μM and 50 mM respectively. Cells were grown for 72h at 27°C and harvested by centrifugation. The cell paste was frozen at –70°C until needed.

EXAMPLE 26

Purification of human Akt1, Akt2, Akt3, ΔPH-Akt1, ΔPH-Akt2, ΔPH-Akt3 and minimal ΔPH Akt1

Cell paste from one liter of S2 cells, described in Example 21, was lysed by sonication with 50 mls 1% CHAPS in buffer A: (50 mM Tris pH 7.4, 1 mM EDTA, 1 mM EGTA, 0.2 mM AEBSF, 10 μg/ml benzamidine, 5 μg/ml of leupeptin, aprotinin and pepstatin each, 10% glycerol and 1 mM DTT). The soluble fraction was

purified on a Protein G Sepharose fast flow (Pharmacia) column loaded with 9mg/ml anti-middle T monoclonal antibody and eluted with 75 μM EYMPME (SEQ.ID.NO.: 20) peptide in buffer A containing 25% glycerol. Akt/PKB containing fractions were pooled and the protein purity evaluated by SDS-PAGE. The purified protein was quantitated using a standard Bradford protocol. Purified protein was flash frozen on liquid nitrogen and stored at -70°C.

Akt and Akt pleckstrin homology domain deletions purified from S2 cells required activation. Akt and Akt pleckstrin homology domain deletions were activated (Alessi et al. *Current Biology* 7:261-269) in a reaction containing 10 nM PDK1 (Upstate Biotechnology, Inc.), lipid vesicles (10 μM phosphatidylinositol-3,4,5-trisphosphate – Metreya, Inc, 100 μM phosphatidylcholine and 100 μM phosphatidylserine – Avanti Polar lipids, Inc.) and activation buffer (50 mM Tris pH7.4, 1.0 mM DTT, 0.1 mM EGTA, 1.0 μM Microcystin–LR, 0.1 mM ATP, 10 mM $MgCl_2$, 333 μg/ml BSA and 0.1mM EDTA). The reaction was incubated at 22°C for 4 hours. Aliquots were flash frozen in liquid nitrogen.

EXAMPLE 27

Akt Kinase Assays

Activated AKT isoforms and pleckstrin homology domain deletion constructs were assayed utilizing a GSK-derived biotinylated peptide substrate. The extent of peptide phosphorylation was determined by Homogeneous Time Resolved Fluorescence (HTRF) using a lanthanide chelate(Lance)-coupled monoclonal antibody specific for the phosphopeptide in combination with a streptavidin-linked allophycocyanin (SA-APC) fluorophore which will bind to the biotin moiety on the peptide. When the Lance and APC are in proximity (i.e. bound to the same phosphopeptide molecule), a non-radiative energy transfer takes place from the Lance to the APC, followed by emission of light from APC at 665 nm.

Materials required for the assay:

A. Activated AKT isozyme or pleckstrin homology domain deleted construct

B. AKT peptide substrate: GSK3α (S21) Peptide #3928 biotin-GGRARTSSFAEPG (SEQ.ID.NO.:21), Macromolecular Resources.

C. Lance labeled anti-phospho GSK3α monoclonal antibody (Cell Signaling Technology, clone # 27).

D. SA-APC (Prozyme catalog no. PJ25S lot # 896067).

E. Microfluor®B U Bottom Microtiter Plates (Dynex Technologies, Catalog no. 7205).

F. Discovery® HTRF Microplate Analyzer, Packard Instrument Company.

G. 100 X Protease Inhibitor Cocktail (PIC): 1 mg/ml benzamidine, 0.5 mg/ml pepstatin, 0.5 mg/ml leupeptin, 0.5 mg/ml aprotinin.

H. 10X Assay Buffer: 500 mM HEPES, pH 7.5, 1% PEG, mM EDTA, 1 mM EGTA, 1% BSA, 20 mM β-Glycerol phosphate.

I. Quench Buffer: 50 mM HEPES pH 7.3, 16.6 mM EDTA, 0.1% BSA, 0.1% Triton X-100, 0.17 nM Lance labeled monoclonal antibody clone # 27, 0.0067 mg/ml SA-APC

J. ATP/$MgCl_2$ working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 125 mM KCl, 5% Glycerol, 25 mM $MgCl_2$, 375 μM ATP

K. Enzyme working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 5% Glycerol, active Akt. The final enzyme concentrations were selected so that the assay was in a linear response range.

L. Peptide working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 5% Glycerol, 2 μM GSK3 biotinylated peptide # 3928

The reaction is assembled by adding 16 µL of the ATP/$MgCl_2$ working solution to the appropriate wells of a 96-well microtiter plate. Inhibitor or vehicle (1.0 µl) is added followed by 10 µl of peptide working solution. The reaction is started by adding 13 µl of the enzyme working solution and mixing. The reaction is allowed to proceed for 50 min and then stopped by the addition of 60 µl HTRF quench buffer. The stopped reactions were incubated at room temperature for at least 30 min and then read on the Discovery instrument.

Procedure for Streptavidin Flash Plate Assay:

Step 1:

A 1 µl solution of the test compound in 100% DMSO was added to 20 µl of 2X substrate solution (20 uM GSK3 Peptide, 300 µM ATP, 20 mM $MgCl_2$, 20 µCi / ml [γ^{33}P] ATP, 1X Assay Buffer, 5% glycerol, 1 mM DTT, 1X PIC, 0.1% BSA and 100 mM KCl). Phosphorylation reactions were initiated by adding 19 µl of 2X Enzyme solution (6.4 nM active Akt/PKB, 1X Assay Buffer, 5% glycerol, 1 mM DTT, 1X PIC and 0.1% BSA). The reactions were then incubated at room temperature for 45 minutes.

Step 2:

The reaction was stopped by adding 170 µl of 125 mM EDTA. 200 µl of stopped reaction was transferred to a Streptavidin Flashplate® PLUS (NEN Life Sciences, catalog no. SMP103). The plate was incubated for >10 minutes at room temperature on a plate shaker. The contents of each well was aspirated, and the wells rinsed 2 times with 200 µl TBS per well. The wells were then washed 3 times for 5 minutes with 200 µl TBS per well with the plates incubated at room temperature on a platform shaker during wash steps.

The plates were covered with sealing tape and counted using the Packard TopCount with the appropriate settings for counting [^{33}P] in Flashplates.

Procedure for Streptavidin Filter Plate Assay:

Step 1:

The enzymatic reactions as described in Step 1 of the Streptavidin Flash Plate Assay above were performed.

Step 2:

The reaction was stopped by adding 20 µl of 7.5M Guanidine Hydrochloride. 50 µl of the stopped reaction was transferred to the Streptavidin filter plate (SAM$^{2™}$ Biotin Capture Plate, Promega, catalog no. V7542) and the reaction was incubated on the filter for 1-2 minutes before applying vacuum.

The plate was then washed using a vacuum manifold as follows: 1) 4 x 200 µl/well of 2M NaCl; 2) 6 x 200 µl/well of 2M NaCl with 1% H_3PO_4; 3) 2 x 200 µl/well of di$H_2$0; and 4) 2 x 100 µl/well of 95% Ethanol. The membranes were then allowed to air dry completely before adding scintillant.

The bottom of the plate was sealed with white backing tape, 30 µl/well of Microscint 20 (Packard Instruments, catalog no. 6013621) was added. The top of the plate was sealed with clear sealing tape, and the plate then counted using the Packard TopCount with the appropriate settings for [^{33}P] with liquid scintillant.

Procedure for Phosphocellulose Filter Plate Assay:

Step 1:

The enzymatic reactions were performed as described in Step 1 of the Streptavidin Flash Plate Assay (above) utilizing KKGGRARTSSFAEPG (SEQ.ID.NO.: 22) as the substrate in place of biotin-GGRARTSSFAEPG.

Step 2:

The reaction was stopped by adding 20 µl of 0.75% H_3PO_4. 50 µl of stopped reaction was transferred to the filter plate (UNIFILTER™, Whatman P81 Strong Cation Exchanger, White Polystyrene 96 Well Plates, Polyfiltronics, catalog no. 7700-3312) and the reaction incubated on the filter for 1-2 minutes before applying vacuum.

The plate was then washed using a vacuum manifold as follows: 1) 9 x 200 µl/well of 0.75% H_3PO_4; and 2) 2 x 200 µl/well of di$H_2$0. The bottom of the

plate was sealed with white backing tape, then 30 µl/well of Microscint 20 was added. The top of the plate was sealed with clear sealing tape, and the plate counted using the Packard TopCount with the appropriate settings for [^{33}P] and liquid scintillant.

PKA assay:

Each individual PKA assay consists of the following components:

A. 5X PKA assay buffer (200 mM Tris pH7.5, 100 mM $MgCl_2$, 5mM β-mercaptoethanol, 0.5 mM EDTA)

B. 50 µM stock of Kemptide (Sigma) diluted in water

C. ^{33}P-ATP prepared by diluting 1.0 µl ^{33}P-ATP [10 mCi/ml] into 200 µl of a 50 µM stock of unlabeled ATP

D. 10 µl of a 70 nM stock of PKA catalytic subunit (UBI catalog # 14-114) diluted in 0.5 mg/ml BSA

E. PKA/Kemptide working solution: equal volumes of 5X PKA assay buffer, Kemptide solution and PKA catalytic subunit.

The reaction is assembled in a 96 deep-well assay plate. The inhibitor or vehicle (10 µl) is added to 10 µl of the ^{33}P-ATP solution. The reaction is initiated by adding 30 µl of the PKA/Kemptide working solution to each well. The reactions were mixed and incubated at room temperature for 20 min. The reactions were stopped by adding 50 µl of 100 mM EDTA and 100 mM sodium pyrophosphate and mixing.

The enzyme reaction product (phosphorylated Kemptide) was collected on p81 phosphocellulose 96 well filter plates (Millipore). To prepare the plate, each well of a p81 filter plate was filled with 75 mM phosphoric acid. The wells were emptied through the filter by applying a vacuum to the bottom of the plate. Phosphoric acid (75 mM, 170 µl) was added to each well. A 30 µl aliquot from each stopped PKA reaction was added to corresponding wells on the filter plate containing

the phosphoric acid. The peptide was trapped on the filter following the application of a vacuum and the filters were washed 5 times with 75 mM phosphoric acid. After the final wash, the filters were allowed to air dry. Scintillation fluid (30 µl) was added to each well and the filters counted on a TopCount (Packard).

PKC assay:

Each PKC assay consists of the following components:

A. 10X PKC co-activation buffer: 2.5 mM EGTA, 4mM $CaCl_2$

B. 5X PKC activation buffer: 1.6 mg/ml phosphatidylserine, 0.16 mg/ml diacylglycerol, 100 mM Tris pH 7.5, 50 mM $MgCl_2$, 5 mM β-mercaptoethanol

C. ^{33}P-ATP prepared by diluting 1.0 µl ^{33}P-ATP [10 mCi/ml] into 100µl of a 100 µM stock of unlabeled ATP

D. Myelin basic protein (350 µg/ml, UBI) diluted in water

E. PKC (50ng/ml, UBI catalog # 14-115) diluted into 0.5 mg/ml BSA

F. PKC/Myelin Basic Protein working solution: Prepared by mixing 5 volumes each of PKC co-activation buffer and Myelin Basic protein with 10 volumes each of PKC activation buffer and PKC.

The assays were assembled in 96 deep-well assay plates. Inhibitor or vehicle (10 µl) was added to 5.0 ul of ^{33}P-ATP. Reactions were initiated with the addition of the PKC/Myelin Basic Protein working solution and mixing. Reactions were incubated at 30°C for 20 min. The reactions were stopped by adding 50 µl of 100 mM EDTA and 100 mM sodium pyrophosphate and mixing. Phosphorylated Mylein Basic Protein was collected on PVDF membranes in 96 well filter plates and quantitated by scintillation counting.

The results from testing the compounds described in Examples 1-19 in the assays described above are shown in Table 5:

TABLE 5

	GSK3 Peptide Substrate IC_{50} (μM)					Counter screens IC_{50} (μM)	
	Akt1	Akt1 delta PH	Akt2	Akt2 delta PH	Akt3	PKA	PKC
Compound 1	1.4	>50	>50	>100	>50	>40	>40
Compound 2	0.42	>50	>50	NA	>50	>40	>40
Compound 3	0.91	>50	>50	NA	>50	>40	>40
Compound 4	2.03	>50	>50	NA	>50	>40	>40
Compound 5	0.4	>50	>50	NA	>50	>40	>40
Compound 6	10.5	>50	>50	NA	>50	>40	>40
Compound 7	3.88	>50	>50	NA	>50	>40	>40
Compound 8	15.9	>50	>50	NA	>50	>40	>40
Compound 9	4.65	>50	>50	NA	>50	>40	>40
Compound 10	2.8	>50	20	>100	>50	>80	>80
Compound 11	6.1	>50	45	NA	>100	>80	>80
Compound 12	4.5	>250	115	NA	>250	NA	NA

TABLE 5 (continued)

	Akt1	Akt1 delta PH	Akt2	Akt2 delta PH	Akt3	PKA	PKC
Compound 13-6	>50	NA	1.75	NA	3.97	>40	>40
Compound 13-7	>17	NA	4.5	NA	>50	NA	NA
Compound 19-11	51.7	>50	>50	NA	1.4	0.076	0.65

EXAMPLE 28

Cell based Assays to Determine Inhibition of Akt/PKB

Cells (for example LnCaP or a $PTEN^{(-/-)}$tumor cell line with activated Akt/PKB) were plated in 100 mm dishes. When the cells were approximately 70 to 80% confluent, the cells were refed with 5 mls of fresh media and the test compound added in solution. Controls included untreated cells, vehicle treated cells and cells treated with either LY294002 (Sigma) or wortmannin (Sigma) at 20 μM or 200 nM, respectively. The cells were incubated for 2, 4 or 6 hrs, and the media removed. The cells were washed with PBS, scraped and transferred to a centrifuge tube. They were pelleted and washed again with PBS. Finally, the cell pellet was resuspended in lysis buffer (20 mM Tris pH8, 140 mM NaCl, 2 mM EDTA, 1% Triton, 1 mM Na Pyrophosphate, 10 mM β-Glycerol Phosphate, 10 mM NaF, 0.5 mN Na_3VO_4, 1 μM Microcystine, and 1x Protease Inhibitor Cocktail), placed on ice for 15 minutes and gently vortexed to lyse the cells. The lysate was spun in a Beckman tabletop ultra centrifuge at 100,000 x g at 4°C for 20 min. The supernatant protein was quantitated by a standard Bradford protocol (BioRad) and stored at –70° C until needed.

Proteins were immunoprecipitated (IP) from cleared lysates as follows: For Akt1/PKBα, lysates are mixed with Santa Cruz sc-7126 (D-17) in NETN (100 mM NaCl, 20 mM Tris pH 8.0, 1 mM EDTA, 0.5% NP-40) and Protein A/G Agarose (Santa Cruz sc-2003) was added. For Akt2/PKBβ, lysates were mixed in NETN with anti-Akt2 agarose (Upstate Biotechnology #16-174) and for Akt3/PKBγ,

lysates were mixed in NETN with anti-Akt3 agarose (Upstate Biotechnology #16-175). The IPs were incubated overnight at 4° C, washed and separated by SDS-PAGE.

Western blots were used to analyze total Akt, pThr308 Akt1, pSer473 Akt1, and corresponding phosphorylation sites on Akt2 and Akt3, and downstream targets of Akt using specific antibodies (Cell Signaling Technology): Anti-Total Akt (cat. no. 9272), Anti-Phospho Akt Serine 473 (cat. no. 9271), and Anti-Phospho Akt Threonine 308 (cat. no. 9275). After incubating with the appropriate primary antibody diluted in PBS + 0.5% non-fat dry milk (NFDM) at 4 °C overnight, blots were washed, incubated with Horseradish peroxidase (HRP)-tagged secondary antibody in PBS + 0.5% NFDM for 1 hour at room temperature. Proteins were detected with ECL Reagents (Amersham/Pharmacia Biotech RPN2134).

EXAMPLE 29

Heregulin Stimulated Akt Activation

MCF7 cells (a human breast cancer line that is $PTEN^{+/+}$) were plated at $1x10^6$ cells per 100mm plate. When the cells were 70 – 80% confluent, they were refed with 5 ml of serum free media and incubated overnight. The following morning, compound was added and the cells were incubated for 1 – 2 hrs , after which time heregulin was added (to induce the activation of Akt) for 30 minutes and the cells were analyzed as described above.

EXAMPLE 30

Inhibition Of Tumor Growth

In vivo efficacy as an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art.

Human tumor cells from cell lines which exhibit a deregulation of the PI3K pathway (such as LnCaP, PC3, C33a, OVCAR-3, MDA-MB-468 or the like) are injected subcutaneously into the left flank of 6-10 week old female nude mice (Harlan) on day 0. The mice are randomly assigned to a vehicle, compound or combination treatment group. Daily subcutaneous administration begins on day 1 and continues for the duration of the experiment. Alternatively, the inhibitor test compound may be administered by a continuous infusion pump. Compound,

compound combination or vehicle is delivered in a total volume of 0.2 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 4 to 5.5 weeks after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

WHAT IS CLAIMED IS:

1. A method for treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of a selective inhibitor of the activity of one or more of the isoforms of Akt.

2. The method according to Claim 1 wherein the selective inhibitor is a small organic molecule.

3. The method according to Claim 1 wherein the selective inhibitor inhibits the phosphorylation of one or more of the isoforms of Akt by upstream kinases and inhibits the phosphorylation of protein targets of an isoform or isoforms of Akt by the activated isoform or isoforms of Akt.

4. The method according to Claim 1 wherein the selective inhibitor inhibits the phosphorylation of one or more of the isoforms of Akt by upstream kinases or inhibits the phosphorylation of protein targets of an isoform or isoforms of Akt by the activated isoform or isoforms of Akt.

5. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1.

6. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt2.

7. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1 and Akt2.

8. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1 and Akt3.

9. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt2 and Akt3.

10. The method according to Claim 2 wherein the inhibitor is a selective inhibitor of the activity of Akt3.

11. A method for treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of an inhibitor of the activity of one or more of the isoforms of Akt wherein the inhibition by the inhibitor is dependent on the presence of the pleckstrin homology domain of the isoforms of Akt.

12. The method according to Claim 11 wherein the inhibitor is a selective inhibitor of the activity of Akt1.

13. The method according to Claim 11 wherein the inhibitor is a selective inhibitor of the activity of Akt2.

14. The method according to Claim 11 wherein the inhibitor is a selective inhibitor of the activity of Akt3.

15. The method according to Claim 11 wherein the inhibitor is a selective inhibitor of Akt1 and Akt2.

16. The method according to Claim 11 wherein the inhibitor is a selective inhibitor of Akt1 and Akt3.

17. The method according to Claim 11 wherein the inhibitor is a selective inhibitor of Akt2 and Akt3.

18. The method according to Claim 11 wherein the inhibitor is a selective inhibitor of Akt1, Akt2 and Akt3.

19. A method for treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of an inhibitor of the activity of one or more of the isoforms of Akt wherein the inhibition by the inhibitor is dependent on the presence of the hinge region of the isoforms of Akt.

20. The method according to Claim 19 wherein the inhibitor is a selective inhibitor of the activity of Akt1.

21. The method according to Claim 19 wherein the inhibitor is a selective inhibitor of the activity of Akt2.

22. The method according to Claim 19 wherein the inhibitor is a selective inhibitor of the activity of Akt3.

23. The method according to Claim 19 wherein the inhibitor is a selective inhibitor of Akt1 and Akt2.

24. The method according to Claim 19 wherein the inhibitor is a selective inhibitor of Akt1 and Akt3.

25. The method according to Claim 19 wherein the inhibitor is a selective inhibitor of Akt2 and Akt3.

26. The method according to Claim 19 wherein the inhibitor is a selective inhibitor of Akt1, Akt2 and Akt3.

27. A method for treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of an inhibitor of the activity of one or more of the isoforms of Akt wherein the inhibition by the inhibitor is dependent on the presence of the pleckstrin homology domain and the hinge region of the isoforms of Akt.

28. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of the activity of Akt1.

29. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of the activity of Akt2.

30. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of the activity of Akt3.

31. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of Akt1 and Akt2.

32. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of Akt1 and Akt3.

33. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of Akt2 and Akt3.

34. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of Akt1, Akt2 and Akt3.

35. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1, but is not an inhibitor of the activity of a modified Akt1 that lacks the pleckstrin homology domain.

36. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt2, but is not an inhibitor of the activity of a modified Akt2 that lacks the pleckstrin homology domain.

37. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt3, but is not an inhibitor of the activity of a modified Akt3 that lacks the pleckstrin homology domain.

38. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1 and Akt2, but is not an inhibitor of the activity of a modified Akt1 that lacks the pleckstrin homology domain, a modified Akt2 that lacks the pleckstrin homology domain or both a modified Akt1 and a modified Akt2 protein that lack their pleckstrin homology domains.

39. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1 and Akt3, but is not an inhibitor of the activity of a modified Akt1 that lacks the pleckstrin homology domain, a modified

Akt3 that lacks the pleckstrin homology domain or both a modified Akt1 and a modified Akt3 protein that lack their pleckstrin homology domains.

40. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt2 and Akt3, but is not an inhibitor of the activity of a modified Akt2 that lacks the pleckstrin homology domain, a modified Akt3 that lacks the pleckstrin homology domain or both a modified Akt2 and a modified Akt3 protein that lack their pleckstrin homology domains.

41. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1, Akt2 and Akt3, but is not an inhibitor of the activity of a modified Akt1 that lacks the pleckstrin homology domain, a modified Akt2 that lacks the pleckstrin homology domain, a modified Akt3 that lacks the pleckstrin homology domain or two or three modified Akt isoforms that lack their pleckstrin homology domains.

42. A method for identifying a compound that is a selective inhibitor of one, two or three of the Akt isoforms, whose inhibitory efficacy is dependent on the pleckstrin homology domain, that comprises the steps of:

a) determining the efficacy of a test compound in inhibiting the activity of an Akt isoform;
b) determining the efficacy of the test compound in inhibiting the activity of the Akt isoform that has been modified to delete the pleckstrin homology domain; and
c) comparing the activity of the test compound against the Akt isoform with the activity of the test compound against the modified Akt isoform lacking the pleckstrin homology domain.

43. A method for identifying a compound that is a selective inhibitor of one, two or three of the Akt isoforms, whose inhibitory efficacy is dependent on the hinge region of Akt, that comprises the steps of:

a) determining the efficacy of a test compound in inhibiting the activity of an Akt isoform;

b) determining the efficacy of the test compound in inhibiting the activity of the Akt isoform that has been modified to delete the pleckstrin homology domain;

c) determining the efficacy of the test compound in inhibiting the activity of the Akt isoform that has been modified to delete the pleckstrin homology domain and the hinge region; and

d) comparing the activity of the test compound against the Akt isoform, the activity of the test compound against the modified Akt isoform lacking the PH domain, and the activity of the test compound against the modified Akt isoform lacking the pleckstrin homology domain and the hinge region.

44. A modified Akt isoform lacking only the pleckstrin homology domain.

45. A modified Akt isoform lacking only the hinge region.

46. A modified Akt isoform lacking the full pleckstrin homology domain and the full hinge region.

47. A method of treating or preventing cancer which comprises administering a selective inhibitor of Akt in combination with a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) a retinoid receptor modulator,
4) a cytotoxic/cytostatic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) PPAR-γ agonists,
12) PPAR-δ agonists,

13) an inhibitor of inherent multidrug resistance,
14) an anti-emetic agent,
15) an agent useful in the treatment of anemia,
16) an agent useful in the treatment of neutropenia,
17) an immunologic-enhancing drug,
18) an inhibitor of cell proliferation and survival signaling, and
19) an agent that interferes with a cell cycle checkpoint.

48. A method according to Claim 47 wherein the second compound is a cytotoxic/cytostatic agent which is an inhibitor of kinases involved in mitotic progression.

49. The method according to Claim 47 wherein the selective inhibitor of Akt is a selective inhibtor of Akt1.

50. The method according to Claim 47 wherein the selective inhibitor of Akt is a selective inhibtor of Akt2.

51. The method according to Claim 47 wherein the selective inhibitor of Akt is a selective inhibtor of both Akt1 and Akt2.

52. A method of treating cancer which comprises administering a therapeutically effective amount of a selective inhibitor of Akt in combination with radiation therapy and a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) a retinoid receptor modulator,
4) a cytotoxic/cytostatic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) PPAR-γ agonists,

12) PPAR-δ agonists,
13) an inhibitor of inherent multidrug resistance,
14) an anti-emetic agent,
15) an agent useful in the treatment of anemia,
16) an agent useful in the treatment of neutropenia,
17) an immunologic-enhancing drug,
18) an inhibitor of cell proliferation and survival signaling, and
19) an agent that interferes with a cell cycle checkpoint.

53. The method according to Claim 52 wherein the selective inhibitor of Akt is a selective inhibtor of Akt1.

54. The method according to Claim 52 wherein the selective inhibitor of Akt is a selective inhibtor of Akt2.

55. The method according to Claim 52 wherein the selective inhibitor of Akt is a selective inhibtor of both Akt1 and Akt2.

SEQUENCE LISTING

<110> Merck & Co., Inc.
Barnett, Stanley F.
DeFeo-Jones, Deborah
Hartman, George D.
Haskell, Kathleen M.
Huber, Hans E.
Nahas, Deborah D.
Lindsley, Craig W.
Zhao, Zhijian

<120> Method of Treating Cancer

<130> 21075Y

<140> 60/417,202
<141> 2002-10-09

<150> 60/370,827
<151> 2002-04-08

<160> 22

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 10
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 1
ctgcggccgc 10

<210> 2
<211> 14
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 2
gtacgcggcc gcag 14

<210> 3
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 3

cgcgaattca gatctaccat gagcgacgtg gctattgtg 39

<210> 4
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 4
cgctctagag gatcctcagg ccgtgctgct ggc 33

<210> 5
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 5
gtacgatgct gaacgatatc ttcg 24

<210> 6
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 6
gaatacatgc cgatggaaag cgacggggct gaagagatgg aggtg 45

<210> 7
<211> 40
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 7
cccctccatc tcttcagccc cgtcgctttc catcggcatg 40

<210> 8
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 8
cgcggcgcgc caggtaccat ggaatacatg ccgatggaaa agaagcagga ggaggaggag 60

<210> 9
<211> 21

<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 9
cggagaacac acgctcccgg g 21

<210> 10
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 10
gaattcagat ctaccatgag cgatgttacc attgtg 36

<210> 11
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 11
tctagatctt attctcgtcc acttgcagag 30

<210> 12
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 12
ggtaccatgg aatacatgcc gatggaaagc gatgttacca ttgtgaag 48

<210> 13
<211> 58
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 13
cgcaggtacc atggaataca tgccgatgga aagcgatgga gaggaagaga tggatgcc 58

<210> 14
<211> 33
<212> DNA
<213> Artificial Sequence

<220>

<223> Completely synthetic DNA Sequence

<400> 14
cgctctagat cttattctcg tccacttgca gag 33

<210> 15
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 15
aagcttagat ctaccatgaa tgaggtgtct gtc 33

<210> 16
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 16
gaattcggat cctcactcgc ggatgctggc 30

<210> 17
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 17
ggtaccatgg aatacatgcc gatggaaaat gaggtgtctg tcatcaaag 49

<210> 18
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 18
cgcaggtacc atggaataca tgccgatgga aaatgagacg actgaggaga tggaagtggc 60

<210> 19
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Completely synthetic DNA Sequence

<400> 19
cgcgaattcg gatcctcact cgcggatgct ggc 33

<210> 20
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Completely synthetic Amino Acid Sequence

<400> 20
Glu Tyr Met Pro Met Glu
1 5

<210> 21
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Completely synthetic Amino Acid Sequence

<400> 21
Gly Gly Arg Ala Arg Thr Ser Ser Phe Ala Glu Pro Gly
1 5 10

<210> 22
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Completely synthetic Amino Acid Sequence

<400> 22
Lys Lys Gly Gly Arg Ala Arg Thr Ser Ser Phe Ala Glu Pro Gly
1 5 10 15

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 2003/084473 A3

(51) International Patent Classification[7]: A61K 31/50, 31/53, 31/495

(21) International Application Number: PCT/US2003/010632

(22) International Filing Date: 4 April 2003 (04.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/370,827 8 April 2002 (08.04.2002) US
60/417,202 9 October 2002 (09.10.2002) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARNETT, Stanley, F.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **DEFEO-JONES, Deborah** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HASKELL, Kathleen, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HUBER, Hans, E.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **NAHAS, Deborah, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **LINDSLEY, Craig, W.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ZHAO, Zhijian** [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HARTMAN, George, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 12 February 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF TREATING CANCER

(57) Abstract: The present invention is directed to a method of treating cancer which comprises administration of a compound which selectively inhibits the activity of one or two of the isoforms of Akt, a serine/threonine protein kinase. The invention is particularly directed to the method wherein the compound is dependent on the presence of the pleckstrin homology domain of Akt for its inhibitory activity.

WO 2003/084473 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/10632

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/50, 31/53, 31/495
US CL : 514/ 243, 248, 249

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/ 243, 248, 249

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,958,773 A (MONIA et al.) 28 September 1999 (28.09.99), column 2, lines 1-40; column 23 line 34 to column 24, line 51; claims 1 and 12.	1-41, 47-55
Y	US 6,043,090 A (MONIA et al.) 28 March 2000 (28.03.00), column 1, line 34 to column 2 , line 5; column 23, line 33 to column 24, line 50; claim 1.	1-41, 47-55
A	US 6,063,783 A (PINEIRO et al.) 16 May 2000 (16.05.00), see entire document.	1-55
A	US 6,110,915 A (CASTRO PINEIRO et al.) 29 August 2000 (29.08.00), see entire document.	1-55

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
16 October 2003 (16.10.2003)

Date of mailing of the international search report
02 DEC 2003

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer
Cybille Delacroix-Muirheid
Telephone No. 703-308-1235

Janice Ford
for

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US03/10632

Continuation of B. FIELDS SEARCHED Item 3:
STN: structure search
akt inhibitor, antagonist, cancer, neoplasms, hinge region, isoform, pleckstrin homology domain